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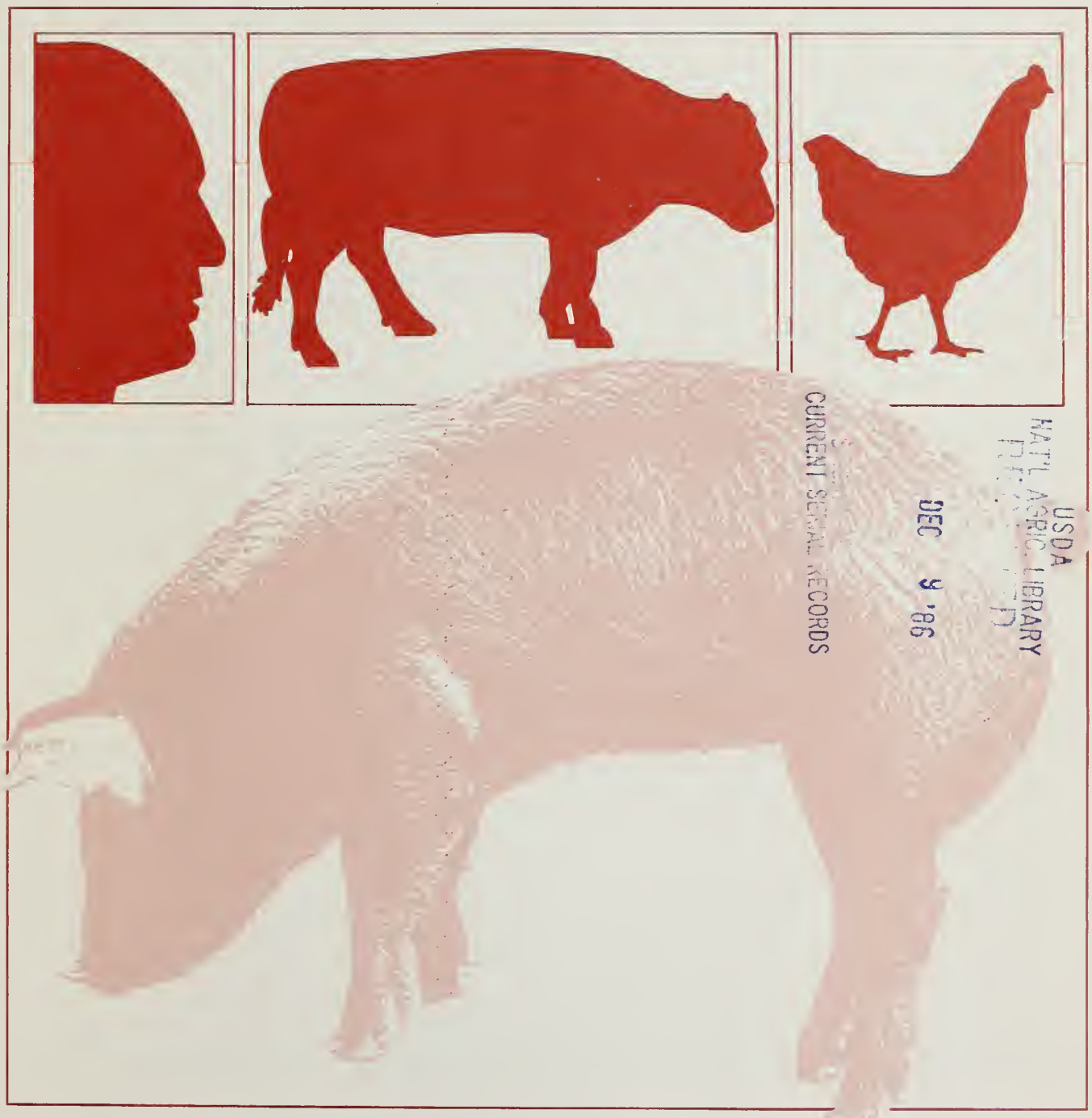

Mycobacterioses in Swine and Their Significance to Public Health

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PREFACE

The impact on mankind of tuberculosis caused by Mycobacterium tuberculosis and Mycobacterium bovis has been on record for many centuries. The disease has claimed many lives and affected the course of history. The control of tuberculosis in humans has been complicated by the fact that both M. tuberculosis and M. bovis can infect domestic animals which may then serve as reservoirs for the disease that can be transmitted to man.

Mycobacteria other than M. tuberculosis and M. bovis have also been shown to occasionally cause disease in humans. A group of organisms, referred to as the M. avium-M. intracellulare-M. scrofulaceum (MAIS) complex, includes the species M. avium, well known as the etiologic agent of avian tuberculosis. Certain organisms within this group have also been found to produce lesions in swine. As a consequence, it has been speculated that swine may also be a source of human infections. This monograph is an effort to provide an answer to that speculation based on scientific evidence accumulated from around the world.

In order to define the possible role of mycobacteria-infected swine and swine tissue as a human health hazard it was necessary to review all available pertinent literature on the subject and to establish the relationships among human and swine infections with members of the genus Mycobacterium.

The confusion in terminology and taxonomic relationships that exists, particularly in the earlier literature, caused considerable problems in organizing and synthesizing the available information.

Historically, the term "tuberculosis" has been loosely applied to the disease caused by M. tuberculosis and M. bovis, as well as those caused by the MAIS complex organisms. The diseases caused by M. tuberculosis or M. bovis have, at times, been referred to as "typical tuberculosis" and their etiologic agents referred to as "tubercle bacilli." The diseases caused by M. avium and other members of the MAIS complex, or even by other species of mycobacteria, have been called "atypical tuberculosis," "pseudotuberculosis," "mycobacterial disease," and the etiological agents have been called as "Battey bacilli," "atypical mycobacteria," "nontubercle bacilli," "pseudotubercle bacilli," or nontuberculous mycobacteria. The term now accepted worldwide, however, for this group of pathogens is mycobacteria other than tubercle (MOTT) bacilli.

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CHAPTER I

INTRODUCTION

The occurrence of tuberculosis in cattle was first recorded in Italy in 14 A.D. However, restrictions on the consumption of meat animals, found in the Mosaic Law and in the Talmud, were probably based on fear of the disease being transmitted from animal to man. For similar reasons the same type of restrictions were applied during the Middle Ages throughout Europe, especially in Germany. The disease was prevalent in Dutch cattle in the 13th century and had spread to English cattle by the 17th century. By the 19th century, as a result of the importation of diseased cattle from Europe, tuberculosis was considered the most destructive disease of American cattle (1).

Laennec, in 1819, was the first to describe tuberculosis of man; and in 1868, Villemin proved that tuberculosis was an infectious disease (2). After Koch discovered the human tubercle bacillus in 1882, Rivolta (1883), and Kline and Gibbs (1898), suggested that the causative organisms of avian and bovine tuberculosis were different from the human bacillus. Later, these organisms were identified as separate from the human pathogen, Mycobacterium tuberculosis, and were named M. avium and M. bovis, respectively (3, 4).

Since humans are susceptible to M. bovis and the organism can be transmitted from person to person, considerable worldwide effort has been directed toward eradicating bovine tuberculosis (5). With improved preventive measures such as the development of the Bacille Calmette-Guerin (BCG) vaccination and the development of effective antibiotic therapy the incidence of classical, or "typical," tuberculosis in humans in the 1950's began to decrease significantly. As a result the occurrence of "atypical mycobacteriosis," while still relatively uncommon, has become more apparent, partly as a result of improved diagnostic procedures (6).

Swine are susceptible to M. tuberculosis, and M. bovis, both of which cause tuberculosis disease in man. Swine are also susceptible to M. avium, and to other mycobacteria related to M. avium that cause nontuberculous disease in man. It is thought by some, therefore, that swine are a possible reservoir of MAIS complex organisms and, as such, responsible for the apparent increased incidence in diseases of man caused by these agents (7-9).

The goal of this monograph is to place in proper perspective the relationship between human mycobacterial infection and the disease in swine caused by certain organisms of the MAIS complex. The monograph is a synthesis of all available pertinent literature on the subject. It describes and differentiates the diseases produced in man and in swine by M. tuberculosis and by MAIS complex organisms, including the epidemiologic manifestations. Finally it discusses the possible role of swine and swine tissue as a hazard to human health.

CHAPTER II

MYCOBACTERIA RESPONSIBLE FOR TUBERCULOSIS OF HUMANS AND SWINE

Tuberculosis of the lungs and other organs was seen and recorded early in the history of mankind. However, the basis for understanding the disease really began with a Dutch physician, Sylvius (1614-72), who named it "phthisis" and described the lesion of the lung as a "tubercle." Since then, many investigators have studied the disease. Villemin (1827-92) was the first to describe tuberculosis as a transmissible disease (10, 11).

Until the middle of the 19th century the occurrence of the disease was thought to be related to such factors as ill health, nutritional deficiency, and foul air. The etiologic agent of the disease was not known until 1882 when Robert Koch isolated M. tuberculosis and conclusively proved his convictions about its etiology with Koch's postulates (2, 11, 12).

In the late 19th and early 20th centuries, pulmonary tuberculosis caused by M. bovis was prevalent in cattle. To prevent transmission of the disease from cattle to man through meat and milk, many countries adopted much needed bovine tuberculosis eradication programs (13).

There is no evidence that swine are a natural host of M. tuberculosis or M. bovis. Infection with these organisms in swine occurs from direct contact with tuberculous humans or cattle. Since swine are susceptible to M. tuberculosis, M. bovis, and M. avium, it is possible that the prevalence of mycobacterial disease in the past in these animals was higher than reports indicated. However, apart from an occasional high prevalence in a particular herd, the total prevalence of tuberculosis in swine never reached the high numbers reported in cattle (1, 14).

DISEASE IN HUMANS

INCIDENCE

For many centuries, pulmonary tuberculosis in man was widespread with a grave clinical outlook (2). A tuberculosis death rate of 400 per 100,000 was common in the 1800's, but in recent years the rate has decreased considerably as a result of drug therapy, better hygiene, improved living conditions, and effective eradication and education programs (15). In the United States the high incidence of tuberculosis dropped sharply from the decade of the 1960's to the 1970's, reflecting the yearly decline in the incidence of new cases as shown in table 1 (16-18). The increased use of a variety of antibiotics and other drugs was a major factor in the rate decline.

DISTRIBUTION

The incidence of tuberculosis infection in the human population has been estimated from the results of tuberculin tests, as well as from reports of active cases. In the United States, 30 percent of the cases are observed in 21 of the largest cities which make up 15 percent of the population.

The rate is higher in impoverished social groups and in certain nonurban groups such as Eskimos. Higher rates in these groups have been attributed to nutritional deficiencies, genetic susceptibility, and overcrowding (15, 18, 19).

Table 1 -- Comparative Rate of Human Tuberculosis, United States, 1960-67 and 1973-80

Year	Total Cases	Rate*	Year	Total Cases	Rate*
1960	55,494	30.8	1973	30,998	14.8
1961	53,726	29.4	1974	30,122	14.2
1962	53,315	28.7	1975	33,989	15.9
1963	54,042	28.7	1976	32,105	15.0
1964	50,874	26.6	1977	30,145	13.9
1965	49,016	25.4	1978	28,521	13.1
1966	47,767	24.4	1979	27,669	12.6
1967	45,647	23.1	1980	27,749	12.3

* Per 100,000 population

PREVALENCE

Since 1900, the prevalence of tuberculosis in the United States has declined considerably. The age of peak incidence has shifted from the young to those over 65. The occurrence of disease in this latter group is largely due to reactivation of old lesions resulting from weakening of the immune response, which in turn may be due to stress, malnutrition, alcoholism, aging, or immunosuppression from drug or disease. Thus, the highest prevalence is seen in the elderly living in nursing homes, and in impoverished persons living alone in city slums. In females there is a higher prevalence in an age group below 65 years of age due to such predisposition factors as pregnancy. The incidence becomes 2 1/2 times higher in both sexes past 65 (20).

MORTALITY

Before the 20th century, clinical tuberculosis cases were usually terminal. Since then, there has been a steady decline in mortality. This decline is attributed to socioeconomic improvement, better nutrition and hygiene, and prevention of transmission. Another major factor has been effective chemotherapy (21, 22).

In 1979, there were 27,669 new cases of tuberculosis and 1,980 recorded deaths in the United States (18). In 1980 it was estimated that as many as 10 million cases of tuberculosis occur throughout the world each year, with 2-3 million resulting death (23).

TRANSMISSION

Although disease caused by M. tuberculosis is transmissible it is relatively difficult for tubercle bacilli to invade the body and establish disease. The bacilli are spread principally by aerosols, droplet nuclei derived from individuals with open pulmonary lesions. Droplet nuclei dry in the air and effectively carry the bacilli past the bronchial cilia to the alveoli. The bacillus is a hardy organism that can survive for weeks in moist or dry sputum. However, it can be killed by a few hours of exposure to sunlight (19).

PATHOGENICITY

The pathogenicity of the organism for a host, the resistance of the host, and the size and site of inoculum all play important roles in the production of the disease. The response by humans to tubercle bacteria invasion varies from a limited lesion to a progressive disease. Because of variable resistance involving local and systemic factors, healing and progressive lesions may exist in the same individual. The disease may often have a chronic cyclical course and may persist for years with exacerbations, remissions, and relapses (24, 25).

THE SYNDROME

Tuberculosis may be manifested as a pulmonary or extrapulmonary disease. The extrapulmonary form is defined by the location of the disease, such as in bones and joints, the endocrine system, lymphatic system, and spleen or urinary tract. The pulmonary infection may simulate signs of a cold with the most frequent sign a cough. Hemoptysis and chest pain may follow. Fever is often not noticed and, when present, usually occurs in late afternoon. Night sweat, loss of weight, dyspnea, and cyanosis are seen in advanced cases (19, 25).

PREVENTION

In past years, mass surveys using tuberculin test and radiographs were conducted to determine the prevalence of disease in a particular area or country. This was followed by the isolation and treatment of positive cases. However, the number of new cases in many countries, including the United States, has fallen so low that these procedures are no longer cost effective. Vaccinations have been used for prevention but not for complete protection. The more commonly used vaccine is Bacille Calmette Guerin (BCG), made from an attenuated strain of M. bovis first introduced in 1921 in France (24). Similarly, the vole bacillus (M. microti) was first used in England in 1940 (25). Both vaccines are injected intradermally. Reactions to the vaccine have been occasionally observed (26).

Vaccination of tuberculin-positive individuals may cause tuberculin hypersensitivity. Tuberculin-positive individuals are, therefore, not usually vaccinated. Vaccination is advised for the tuberculin-negative individual who has a high risk of infection (15, 26, 27, 28). The occurrence of tuberculosis infection in vaccinated persons in India has raised doubt as to the effectiveness of this preventive measure (23).

DISEASE IN SWINE

In the early 1900's, a spokesman from the U.S. livestock industry warned veterinarians and sanitarians about swine "tuberculosis," presumably due to M. tuberculosis, because of greater losses from this disease than from hog cholera. Over the years, the disease in swine has not been considered as serious a problem as in cattle. As a result of the eradication program in cattle, the prevalence of the disease in both cattle and swine has decreased in recent years; however, the decline in swine has not been as pronounced as in cattle. In the United States, 1,645 (0.005 percent) of 30,882,588 cattle slaughtered in 1980 had tuberculosis-like lesions. In contrast, 622,786 (0.69 percent) of 90,037,586 swine slaughtered had lesions, regarded under the present meat inspection regulations as associated with tuberculosis (29). However, these data from USDA reports do not distinguish between lesions caused by the tubercle bacilli, M. tuberculosis or M. bovis, and mycobacteria other than tubercle (MOTT) bacilli. In 1984, although the percentage of carcasses with tuberculosis-like lesions was 138 times higher in swine than in bovines, it reflected a decrease from 12 years earlier (30).

PREVALENCE

The United States has never had a national program to detect or eradicate tuberculosis from live swine. Thus, the data on the prevalence rate of the disease in the United States is based entirely on the lesions detected in slaughtered animals and noted in inspection records. In 1922, it was reported that 16.38 percent of swine carcasses inspected had tuberculosis lesions, and only 0.2 percent of these carcasses were condemned (14). Since that time, the rate has declined gradually. In 1971, less than 1 percent of the carcasses reportedly had tuberculosis lesions and only 0.006 percent of those were condemned (table 2).

DISTRIBUTION

The prevalence of swine TB reported in the 1930's varied widely with the geographic location. Swine TB retention rates were 15.09 percent and 11.35 percent for the St. Paul and Chicago slaughterhouses, respectively, compared with 6.8 percent and 4.9 percent for the St. Louis and Kansas City slaughterhouses (31). During the next 20 years the rates for St. Paul and Kansas City decreased to 3.07 percent and 2.5 percent, respectively (32). Since most cases of TB in swine were thought to be caused by M. avium, it was suggested that the higher rate of retention of swine carcasses, due to TB lesions, was directly related to the higher rate of avian TB in the North-Central States than in other parts of the United States (33). In 1968, 88 percent of the condemnations of chickens were reported from the North-Central States (34).

In spite of higher prevalence rates of TB in swine in the North-Central States, early researchers were reluctant to accept a geographical effect on the incidence of the disease. Their objection was based on the uncontrolled swine movement from one State to another (33). The rate in the last 4 years for all regions in the United States as presented in table 3 indicates higher prevalence for Southeastern and Northeastern States (35).

Table 2 -- Prevalence of Tuberculosis in Swine, United States, 1970-80

Year	Animals Slaughtered	Percentage With Tuberculosis Lesions	Percentage Condemned For Tuberculosis
	Number	Percent	Percent
1970	73,657,941	1.208	0.006
1971	85,697,847	.822	.006
1972	83,108,614	.878	.007
1973	75,626,750	.912	.008
1974	73,870,169	.921	.008
1975 1/	32,987,667	.900	.008
1976	70,932,790	.753	.006
1977	69,945,417	.671	.007
1978	71,808,911	.802	.006
1979	83,323,703	.769	.006
1980	90,037,586	.681	.005

1/ January-June only

Sources: Food Safety and Quality Service, Meat and Poultry Inspection Program, USDA (30).

Food Safety and Inspection Service, Meat and Poultry Inspection Program, USDA (29).

Table 3 -- Prevalence and Condemnation of Tuberculous Swine Carcasses United States, by Region, 1977-80

Region	Prevalence				Condemnation			
	1977	1978	1979	1980	1977	1978	1979	1980
	Percent							
Western	0.87	0.73	0.81	0.85	0.012	0.005	0.008	0.005
Southwestern	.46	.47	.36	.30	.005	.006	.003	.002
North-Central	.58	.62	.56	.50	.006	.007	.006	.006
Southeastern	1.03	1.20	1.20	.97	.009	.008	.005	.005
Northeastern	1.50	1.80	1.70	1.60	.006	.003	.003	.003

Source: Meat and Poultry Inspection, Program, FSIS, USDA (35)

ETIOLOGY

The condemnation rates for tuberculosis in swine, reported as tuberculosis, did not vary significantly within regions for 4 years (table 3). Some scientists, however, are skeptical of the use of these data for determining the prevalence of the disease because they are derived from meat inspection records based primarily on the gross examination of the lesion(s) from a carcass. It is true that lesions that are not grossly visible are not detected. However, meat and poultry inspection records indicate that 90 percent of the specimens that are detected and submitted by the inspectors are found by Food Safety and Inspection Service (FSIS) laboratories to be positive for "tuberculous lesions" by histopathological examination (36).

Microscopic examination of the node, together with culturing of the node, improves the chances of positive diagnosis of the lesion (37-43). Failure to isolate the bacilli may result from long shipment time, inadequate shipping or culturing methods, lack of expertise, state of the lesions, absence of bacilli, or similarity of inflammatory lesions produced by some other micro-organisms. More recent attempts at isolating organisms from lesions have also met with varying degrees of success (table 4).

Table 4 -- Isolation of Mycobacteria from Swine Lesions

Country of Origin	Specimens	Success in Isolation	References
	Number	Percent	
United States	200	97.5	(37)
United States	78	87.3	(38)
United States	2,625	73.1	(39)
United States	40	90.0	(40)
Denmark	32	62.5	(41)
Denmark	18	55.5	(42)
Hungary	121	62.8	(43)

THE SYNDROME

Generalized tuberculosis in swine is seldom seen clinically. However, in the disseminated condition, signs of generalized infection, such as rise of body temperature, anorexia, loss of weight, coughing progressing to dyspnea, diarrhea, and meningitis are seen. In some cases, pressure on motor nerves by enlarged lymph nodes results in paralysis. Enlargement of peripheral lymph nodes, arthritis, orchitis, and mastitis can occur, and nodes may ulcerate to form draining sinuses. Metritis due to tuberculosis can lead to vaginal discharge (14, 44).

PATHOLOGIC MANIFESTATIONS

The extent of the lesions varies with the age of the animal. The lesions may range from a few small foci in several organs, to multiple nodular processes seen in the liver, spleen, lungs, kidney, and lymph nodes. Lesions due to the avian type are diffuse and generally there is no encapsulation by fibrosis. In some cases, foci of caseation are observed but no pronounced calcification is noted. With mammalian bacilli, the lesions are comparatively discrete, caseous, and are well defined by fibrosis. They are usually confined to the pharyngeal, cervical, and mesenteric lymph nodes, varying in size and appearance depending on the colonization of the bacterium in the tissue. In earlier stages, the lesions vary from small pinpoint yellowish-white caseous foci to a diffuse enlargement of the entire node. The lesions may be seen in one group of nodes or may involve a number of lymph nodes along the digestive tract (45).

In most cases, it is difficult to differentiate grossly tuberculous lymphadenitis caused by avian or mammalian bacilli. However, in some infections of avian origin, nodes may be enlarged, firm with purulent foci, or there may be a few caseous foci with no sharp outline. The incised surface has a neoplastic appearance. Sometimes there are a few caseous foci with large amounts of fibrosis but no evident encapsulation (14, 44, 45).

Microscopically, infection in swine tissue by avian tubercle bacteria causes diffuse proliferation of epithelioid cells and giant cells. In older lesions, necrosis and calcification may be seen. Usually there is proliferation of connective tissue devoid of a defined boundary. The lesions due to mammalian tubercle bacteria have encapsulated and well-developed zones of connective tissue. Also, in these lesions there is early caseation and marked calcification (14, 45).

TRANSMISSION

Swine are known to be susceptible to all three species of mycobacteria responsible for tuberculous disease in humans, other mammals, and birds. The tuberculosis disease of swine has been reported to be a result of direct or indirect association with cattle, poultry, or humans, carrying infections of *M. bovis*, *M. avium*, and *M. tuberculosis* respectively (46-47).

In the 1930's when prevalence of tuberculosis in cattle was high, *M. bovis* was more frequently isolated from tuberculosis lesions in swine (46-47). However, with bovine TB eradication programs, the prevalence of TB in cattle decreased considerably. Simultaneously the frequency of isolation of *M. bovis* and *M. tuberculosis* from swine also decreased considerably. In recent years, only rare incidents of *M. bovis* and *M. tuberculosis* infection in swine have been reported. *M. avium* is mainly responsible for the disease in swine, as shown in table 5.

The occasional finding of *M. bovis* in swine TB outbreaks implicates cattle as being a potential source of organisms. As early as 1899 unpasteurized milk from infected cattle was suspected of transmitting the disease in swine (14). Uncooked offal from tuberculous cattle has also been shown to harbor the pathogen and cause outbreaks in swine (46). Close contact between swine and

cattle and among swine in yards and feeding pens does provide an opportunity for transmission of organisms from animal to animal (14).

Table 5 -- Species of Mycobacteria Associated with Swine Tuberculosis, Selected Countries and Years

Country	Period	Mycobacterium Species			References
		avium (complex)	bovis	tuber-culosis	
			1/		
Belgium	1940-50	--	99	--	(48)
Denmark	1955	--	99	--	(49)
Great Britain	1952-66	80	20	--	(50)
W. Germany	1971	42	2.8	0.2	(51)
Rumania	1971	57	40	--	(52)
W. Germany	1973	100	--	--	(53)
France	1972-74	100	--	--	(54)
W. Germany	1974	100	--	--	(55)
Yugoslavia	1974	99	--	--	(56)
Czechoslovakia	1974	60	--	--	(57)
United States	1975	99	--	--	(37)
United States	1975	92	--	--	(58)
Denmark	1977	62.5	--	--	(41)
United States	1977	90	--	--	(59)
Japan	1979	99	--	--	(60)
United States	1980	85	--	--	(61)

1/ Figures equal percentage

Infection of the cervical and mesenteric lymph nodes in a majority of cases indicates the route of infection to be oral. Variation in the site of infection is quite significant as shown by a 1937 survey where 2.7 percent involve the lung and 97.3 percent involve the alimentary tract (47). Data on the prevalence of tuberculosis in swine for 1970-80 indicate a decrease in both the rate of TB lesions in swine carcasses and the rate of condemnation due to tuberculosis (table 2).

CONTROL

There has never been a direct campaign conducted in the United States to eradicate the disease from swine. In 1900, when TB caused by M. bovis was prevalent in cattle, it was thought that eradication of the disease in cattle would automatically reduce the incidence in swine (45). However, over the years, as a result of the TB eradication program, the incidence of TB decreased drastically in cattle, but the rate of condemnation of swine carcasses due to TB lesions did not decline significantly. The rate in swine

did not show a decline because the majority of the cases in swine were not caused by M. bovis, but were caused by M. avium. It was presumed that the rate of tuberculosis in swine would decrease if the occurrences in poultry were kept under control (2, 14).

At one time, when the majority of the infections were suspected to be due to M. bovis, the possibility of controlling tuberculosis in swine by BCG vaccination was discussed occasionally. However, under experimental conditions, BCG has failed to protect swine against artificially induced disease (62).

CHAPTER III

MYCOBACTERIA OTHER THAN TUBERCLE (MOTT) BACILLI ASSOCIATED WITH THE DISEASES OF HUMANS AND SWINE

In the early 1900's mycobacteria other than M. tuberculosis, M. bovis, and M. avium were thought to be nonpathogens (63). As the rate of isolation of nontuberculosis mycobacteria increased, the possible involvement of nontuberculous acid-fast bacilli in disseminated disease entities was given close consideration. Since the 1940's involvement of "atypical" mycobacteria in diseases of humans and animals has been reported (39, 64-68). Because of some antigenic and biochemical similarity between strains, some are grouped as Mycobacterium avium-M. intracellulare-M. scrofulaceum (MAIS) complex organisms (9, table 6). Pathogens belonging to several serovars have been isolated from lesions of swine. Consequently, some investigators have thought that swine could possibly be the reservoir of these serovars, and might also be responsible for transmission of mycobacterial infection to humans.

MOTT BACILLI IN HUMAN DISEASE

Mycobacterium avium and Mycobacterium intracellulare (Mycobacterium avium complex): In 1890, it was recognized that Mycobacterium avium was responsible for disease in chickens and was different from mycobacteria responsible for human tuberculosis. Although humans are reported to be relatively resistant to M. avium (9), there are reports that some serotypes of M. avium organisms were responsible for disseminated disease in man (65-68). The number of reported cases is small. According to a recent worldwide review of literature on M. avium infections in man, only a few hundred clinically significant cases were reported between 1892 and 1976 (69).

The resemblance between M. avium and M. intracellulare is so strong that distinction between the two species requires special competence and for this reason, serotypes belonging to both are grouped as M. avium complex. Studies indicate that serotypes 1, 2, and 3 usually are fully pathogenic for chickens, in most instances resembling typical M. avium, whereas serotypes 4 through 6 and 8 through 11 have variable degrees of virulence and are termed "intermediates." Strains belonging to serotypes 12 through 28 are usually not pathogenic and are placed in the intracellulare group (70, 71). Of 28 serotypes found in the complex, type 8 is the one most commonly recovered from man and animals (9). Common isolates from man have varying degrees of pathogenicity for rabbits and guinea pigs (70, 72, 73).

Since the 1950's it has been regularly observed that about 1 percent to 3 percent of the patients in tuberculosis hospitals had a peculiar type of Mycobacterium in their sputum, the characteristics of which were different from M. tuberculosis (66). The organisms were later identified as M. avium-M. intercellulare (M. avium complex). They were isolated from lymph nodes, biopsies, and from tissues of dead humans, and had variable pathogenicity for laboratory animals. Most isolates were found tobe resistant to antituberculous drugs but were often sensitive to rifampin and streptomycin (74, 75).

Guinea pigs sensitized with the "Boone" strain of Mycobacterium intracellulare presented large reactions to homologous Purified Protein Derivative-B (PPD-B) and almost equally large reactions to PPD-A. However, they showed less

extensive cross-reactions with scrofulin and progressively less with tuberculin, kansasiin, and fortuitin (76). Based on skin test results it has been suggested that the frequency of exposure to M. intracellulare complex is greater than to M. tuberculosis but less than to M. scrofulaceum. M. intracellulare infection has frequently been reported in mycobacterial pulmonary disease and less frequently as the cause of lymphadenitis in children. The symptoms and radiographic findings are indistinguishable from those in patients with classical M. tuberculosis infection (67, 77).

Table 6 -- Mycobacterial Serotypes of M. avium, M. intracellulare, and M. scrofulaceum Recognized by Agglutination

Complex or Species	Types, by Number	Types, by Old Name or Old Number	
M. avium complex			
"avium" types	1,2,3	M. avium I,II,III	
"intracellulare" types	4	IV	
	5	V	
	6	VI	
	7	VII	
	8	Davis	
	9	Watson	
	10	IIIa	
	11	IIIb	
	12	Howell	
	13	Chance	
	14	Boone	
	15	Dent	
	16	Yandle	--- MAIS Complex
	17	Wilson	
	18	Altman	
	19	Darden	
	20	Arnold	
	21,22		
	23	Brockett	
	24,25		
	26	Cox	
	27	Harrison	
	28		
"scrofulaceum" types	41	scrofulaceum	
	42	Lunning	
	43	Gause	
	44	Cole	

These complexes of organisms have been isolated from the bronchial secretions and saliva of both healthy and sick individuals. It suggests that the environment, such as the soil and water, may be the source of these organisms. From these sources they are ingested or are carried in the air and inhaled as pulmonary "bugs" (78). M. avium-M. intracellulare is the most common cause of atypical mycobacterial pulmonary infection in humans in North Carolina, Georgia, and Florida (66, 77).

Mycobacterium scrofulaceum: Because of the similarity of biochemical reactions, surface antigens, drug resistance, and variable pigmentation between M. intracellulare and M. scrofulaceum, it has been suggested that M. scrofulaceum could be regarded as a pigmented form of M. intracellulare (79). This may be the reason that the acronym, MAIS complex, is now being used for the group of organisms belonging to the M. avium-M. intracellulare-M. scrofulaceum serotypes (80, 81). Some clinical strains that produced in vitro reactions intermediate between M. avium and M. scrofulaceum were not typeable by seroagglutination test (82). In the 1960's similar strains were labeled "pigmented Batteys" or Group III B type as opposed to the nonpigmented type belonging to Group III A (83). Species-specific antigens of M. scrofulaceum and M. avium have been detected by immunodiffusion tests (84, 85). M. scrofulaceum produces colonies that are yellow-orange in the dark and that become more reddish when grown in light. Growth is slow, as with M. tuberculosis, and yields smooth, soft colonies which become dome shaped with age (86).

Strains of M. scrofulaceum, identified serologically, are frequently found as the sole etiologic agent in cervical lymphadenitis in young children (87). A skin test survey in the United States with a dose of 0.0001 mg of PPD-B (Boone strain) gave positive reactions in 50 percent of Navy recruits and medical students (88). In the past, the "tap water bacillus," M. gordonae, was indistinguishable from M. scrofulaceum by colony morphology, pigment production, and catalase reaction but studies have clarified the distinction between these species (89). Fifty percent of the strains responsible for causing lymphadenitis in children have been classified by seroagglutination into one of three serotypes (90). Strains encountered in Europe are mostly serotype 41 with a lesser number belonging to serotypes 42 and 43. In the United States a large number were serotype 42, and some reacted with the M. avium complex antisera (9). Strains of M. scrofulaceum have been isolated from raw milk (91-92), oysters (93), dairy sludge (94), soil (95), and water (96).

Mycobacterium kansasii: In some areas of the world this species has been found to be a major cause of pulmonary tuberculosis other than that attributable to M. tuberculosis (77). It is easily recognized by its ability to form photoactive pigment and infrequently by the appearance of red crystals of b-carotene on prolonged exposure to light. The presence of large cross-barred acid-fast bacilli in the sputum is often suspected to be evidence of M. kansasii infection (9, 77, 86).

All pathogenic strains of M. kansasii seem to have uniform antigenic structures (97), and there is only one type by seroagglutination (98). In vitro, most strains are susceptible to rifampin and are only slightly resistant to isoniazid and streptomycin (99). A vaccine prepared from M. kansasii seems to have a protective effect against M. tuberculosis infection in guinea pigs (100).

The reservoir for M. kansasii has not been precisely identified. It has been isolated from water samples (101-104) and occasionally from cattle (105) and swine (106). Most evidence points to the fact that it is waterborne and can grow and live in water tanks (101, 103, 104).

Mycobacterium fortuitum complex (M. fortuitum-M. chelonae): This group is comprised of soil organisms which can be isolated readily from soil on ordinary media. They grow rapidly at temperatures ranging from 25° to 40 °C. The colonies can be smooth or rough and are usually nonpigmented (74). By seroagglutination, two types of M. fortuitum and one type of M. chelonei have been detected (107). However, by immunodiffusion, seven different serotypes and two distinct lipid patterns of M. fortuitum have been reported (108).

Most strains in this complex are resistant in vitro to antituberculous drugs, but some were found to be sensitive to a single or combination of broad spectrum antibiotics (109). Human diseases associated with M. fortuitum complex consist mainly of soft tissue abscesses and wound infections (110).

Mycobacterium xenopi: This organism was first isolated in 1957 from a skin lesion of a South African toad (111). Although the organism was first isolated from a cold-blooded animal, and later from the sputum of a patient in England, its optimum temperature for growth is 42 °C. The cells are longer and tapered at both ends. The colony is often yellow in color with age and sometimes exhibits branching forms. The species has been found to have four species-specific antigens, by double diffusion assay in agar, and is sensitive to isoniazid and streptomycin (112).

MOTT BACILLI IN SWINE DISEASE

Based on meat inspection records and reports, swine have been thought to be sensitive to infections with M. tuberculosis or M. bovis arising from humans or from cattle. In the 1930's, this was thought to be the only reason for a higher rate of tuberculosis in swine than in cattle.

The acid-fast bacteria isolated from tuberculous lesions of swine were referred to as Mycobacterium suis by some investigators, but were later shown not to be different from M. avium (113). In the middle 1960's, the presence of M. avium and M. avium-like mycobacteria in lymphadenitis of swine generated more interest in the etiology of the disease (114). Since 1970, it has been found that the higher rate in swine is primarily due to a group of organisms known as the M. avium complex (table 5).

Some scientists are of the opinion that disease in swine caused by the M. avium-M. intracellulare-M. scrofulaceum (MAIS) complex, or any other mycobacteria other than tubercle bacilli, should be addressed as "mycobacteriosis." In the same way, disease conditions should be identified as "tuberculosis" when evidence suggests M. tuberculosis or M. bovis as the causative agent (115).

Based on the degree of virulence of the swine isolates, three groups of infectious agents in swine have been suggested: M. avium, M. tuberculosis, and Group III mycobacteria of intermediate virulence (116). Various species of mycobacteria isolated from swine during post-mortem examination indicate that the above hypothesis probably is true (table 7).

Table 7 -- Species of Mycobacteria Involved in Swine Mycobacteriosis, by Country

Country and Year	Mycobacteria	Number Isolated	References
Germany, 1968	M. avium	133	(117)
	M. kansasii / M. avium	1	
	Group II / M. avium	2	
	M. fortuitum / M. avium	2	
	M. kansasii	1	
	Group II	7	
	M. intracellulare	2	
	M. fortuitum	7	
	M. tuberculosis	3	
	M. bovis	6	
Finland, 1968	M. kansasii	6	(118)
	M. gordanae	20	
	M. gordonae var. ureolyticum	6	
	M. avium	86	
	M. phlei	*	
	M. smegmatis	*	
	M. tuberculosis	3	
France, 1968	M. avium	*	(119)
	M. bovis	*	
Holland, 1967	M. microti	*	(120)
Norway, 1936	M. avium	80	(121)
	M. tuberculosis	16	
	M. bovis	1	
Norway, 1936	M. paratuberculosis	*	(122)
Finland, 1965	C. equi	*	(123)
U. S., 1971	M. avium	24	(124)
	Battey type	1	
Japan, 1977	M. avium-M. intracellulare complex	113	(125)
Japan, 1976	M. avium-M. intracellulare complex	100	(126)
	M. fortuitum	16	

(continued)

Table 7 -- Species of Mycobacteria Involved in Swine Mycobacteriosis, by Country -- Continued

Country and Year	Mycobacteria	Number Isolated	References
Brazil, 1978	M. avium-M. intracellulare complex	7	(127)
	M. gordonae	2	
	M. flavescens	2	
	M. terrae complex	14	
	M. fortuitum	3	
U. S., 1975	M. avium	1547	(39)
	M. bovis	15	
	M. scrofulaceum	1	
	M. fortuitum	3	
	M. xenopi	1	
	M. paratuberculosis	1	
	Mycobacterium spp	23	
Canada, 1976	M. intracellulare	20	(128)
Japan, 1973	M. fortuitum	3	(129)
	M. tuberculosis	1	
	M. intracellulare	16	
	M. scrofulaceum	4	
U. S., 1979	M. avium-M. intracellulare complex	46	(130)
	M. gastri	1	
Poland, 1974	M. avium	106	(131)
	M. intracellulare	1	
	M. scrofulaceum	1	
	M. terrae	3	
	M. tuberculosis	1	
	M. vaccae	3	
Sweden, 1979	M. avium-M. intracellulare complex	50	(132)
Denmark, 1977	M. intracellulare	8	(42)
France, 1976	M. avium	9	(133)
	M. gordonae	4	
	Unknown	1	

* Exact number of isolates not reported

MAIS Complex: The mycobacterial isolates identified in table 7 were mainly from animals slaughtered for human consumption. Only occasional clinical cases of swine mycobacteriosis have been reported. In these cases the organisms were isolated to establish the etiology (80, 134, 135).

Reports (table 7) indicated that in the last 15 years in many parts of the world, including the United States, strains of the M. avium complex have generally been responsible for the disease in swine labeled as "tuberculosis." In the 1950's, because of the limited knowledge of the identity of these organisms, some of the slow-growing mycobacteria were variously labeled as M. intracellulare, M. avium, Battey avian complex, or Avian-Battey group of mycobacteria (6). Strains of M. avium and M. intracellulare resemble each other so strongly that most laboratories cannot distinguish them. They have often been referred to as the M. avium-M. intracellulare complex. Also, because of variability of pigmentation in both M. avium and M. scrofulaceum, some similarity of biochemical reactions, surface antigens, and drug resistance between the two, M. scrofulaceum has been grouped with the M. avium complex to form the MAIS complex (9, table 6). Additionally, lipid analysis of M. scrofulaceum indicates that the organism could be regarded as a pigmented type of M. intracellulare (79).

Data (tables 5 and 7) indicate that a majority of swine mycobacteriosis cases of the past, often misrepresented as "tuberculosis," were due to the MAIS complex (81). This fact was well documented over a 3-year study period (1971 through 1974) in the United States in which 87 percent of mycobacteria involved in tuberculous lymphadenitis of swine were identified as members of the MAIS complex group (39). A report of other studies in other parts of the world also indicates that organisms belonging to the MAIS complex group were mainly associated with diseases in swine (48).

There are at least 32 serotypes in the MAIS complex (table 6), with additional reports of new serotypes to be included in this group (126). Studies on swine isolates in the United States indicate that serotypes 1 and 2 account for the majority of the isolates (table 8). Similarly, serotypes 1 and 2 are prevalent in France and Poland. Serotypes 4, 8, and 10 were also isolated in appreciable numbers in the United States. Serotype 8 was found prevalent in Japan, and serotypes 6, 7, and 8 in Brazil. In general, it can be noted that the isolation rate for serotype 2 is twice the rate of serotype 1. Also, some of the isolates reacted to two different antisera, and some organisms were not typeable.

In addition to localized tuberculous lymphadenitis of swine, M. avium serotype 1 was incriminated in a swine abortion case in the United States (140).

Mycobacterium fortuitum: This organism has been isolated from porcine lymph nodes in the absence of clinical symptoms (141, 142).

Mycobacterium xenopi: This organism has been isolated only once from a lesion in the mesenteric lymph node of a pig. The antigenic character of the isolate was found to be similar to M. avium serotype 1. However, the antigenic components were found to be common with those of M. intracellulare. The organism was identified as a pathogen and was responsible for a granulomatous lesion in the lymph node (143).

Table 8 -- Number of M. avium-M. intracellulare-M. scrofulaceum, (MAIS) Complex Isolates, by Serotype, from Swine Tissue, in Various Countries

Country	References	MAIS Complex Serotypes																						
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19---23	A*	B*	C*	D*
United States	(136)	43	86	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	60
Sweden	(41)	—	2	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Japan	(137)	—	—	—	1	—	—	—	63	—	3	—	—	—	—	—	—	—	—	—	—	1	2	—
Poland	(131)	6	98	2	1	—	—	—	1	—	1	—	—	—	—	—	—	—	—	—	—	—	—	—
United States	(39)	452	728	3	60	5	2	3	110	13	51	1	3	—	2	—	1	1	2	—	65	45	—	—
United States	(37)	92	82	—	2	—	—	—	5	1	—	—	—	—	—	—	—	—	—	—	3	10	—	—
United States	(59)	1	15	—	—	—	—	—	3	—	—	—	—	—	—	—	—	—	—	—	2	—	—	—
Japan	(126)	—	—	1	9	—	—	—	70	7	2	—	—	—	—	1	—	—	2	—	—	4	7	—
United States	(38)	36**		—	7	—	—	—	7	—	9	1	1	—	—	—	—	—	—	—	—	—	—	—
Germany	(138)	72	492	—	10	—	—	—	105	42	2	—	—	—	—	—	—	—	—	—	7	—	—	—
Brazil	(127)	—	—	—	3	—	18	10	19	—	3	—	3	1	2	1	—	—	—	—	—	9	—	—
Sweden	(132)	1	4	9	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	7	—	—
France	(139)	7	58	1	—	—	—	—	1	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—
United States	(61)	1	—	—	2	—	—	—	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	TOTALS	711	1565	16	95	5	20	13	385	64	71	2	7	1	4	2	1	1	4	-	77	76	9	60

* A = Double; B = Untypeable; C = (T96, 116); D = Not typed
** Combination of serotypes 1 and 2

CHAPTER IV

MYCOBACTERIOSIS IN HUMANS AND SWINE

Mycobacteria other than M. tuberculosis, M. bovis, and M. avium, detected for many years in clinical specimens from humans, were considered saprophytes (144). In 1935, a possible cause-effect relationship between this group of bacteria and human illness was suggested (145) and later confirmed (146). By 1954, a number of these clinical isolates were primarily classified and identified as "atypical" mycobacteria, a group separate from those previously known to cause disease in mammals and birds (67). Since 1957, many case histories, narratives on the clinical symptoms and the etiology associated with the diseases, have been reported (9, 69, 147).

Like classical tuberculosis in man, infection by these organisms may cause acute or chronic infection. The infection can be pulmonary or extrapulmonary and can be fatal. Commonly, the disease is associated with predisposing factors, the course is relatively benign, and the symptoms in the beginning are mild. However, fever, pleuritic pain, serous hemoptysis, or other complications may occur in the pulmonary form. Physical findings may vary with the severity of the disease. Symptoms may or may not always be correlated with the findings. Except for bacteriological investigation leading to the identification of acid-fast organisms in clinical specimens, other clinical tests are not very conclusive (66, 67, 77, 148).

There are several important clinical problems associated with infection by these groups of organisms. In some cases, the organisms have been found to be associated with a specific lesion at a specific site. Thus, the site of infection involving different tissues or organs is taken into consideration in diagnosing the disease.

DISEASE IN HUMANS

LUNG LESIONS

Chronic disease of the lung in man is probably the most important clinical syndrome that has been found associated with "atypical" mycobacterial infection (65, 149-159). Among all the types, M. kansasii (152-154) and M. avium-M. intracellulare are the most common pathogens associated with this site (68, 155-159). Pulmonary disease by other mycobacterial species (160-163), M. scrofulaceum (164-167), and M. fortuitum-M. chelonei has been documented (168-179).

As in classical tuberculosis of the lung, the clinical signs associated with MOTT bacilli vary greatly depending upon the severity of the disease. The disease can be asymptomatic with a minimal lesion, detected by X-ray only as a "nodule," or not at all. These nodules must be 5 mm in diameter before radiography can detect them. The presence of blood in the sputum in advanced, severe, cavitary cases has also been observed. However, there are subtle differences between the symptoms of tuberculosis and mycobacteriosis which may be recognized by experts. The etiology of the disease is established only by the identification of the mycobacteria in culture (9, 66, 77). On the average, a case of pulmonary disease caused by M. kansasii or M. avium complex

would be encountered in a white male past 45 years of age with a chronic lung condition, such as bronchitis or silicosis. Symptoms would include dry cough, night sweats, low-grade fever, and moderate weight loss. Radiographs would indicate fibrosis and a thin-walled cavity in the right upper lobe and the sputum would be positive for acid-fast bacilli. Only in rare instances would some other member of the patient's family present the same clinical symptoms. Usually there would be no family history, or obvious source, of an M. tuberculosis infection (9, 77, 159).

Since 1965 several cases caused by M. xenopi have been reported (177-181). The clinical symptoms associated with M. xenopi infection are not very different from the symptoms produced by M. tuberculosis (9, 77).

Only a very small number of pulmonary cases caused by M. scrofulaceum have been reported. The disease has been reported mostly in men with evidence of long-term exposure to industrial dust. The etiology of the disease was established by the histopathological and bacteriological examination of resected lung tissue (165-167).

In some cases rapidly growing strains of mycobacteria, such as the M. fortuitum complex group, probably cause pulmonary infection in those individuals who also suffer from chronic bronchitis, rheumatoid arthritis, pneumonia, pleurisy, or alcoholism (173).

LYMPHADENITIS

In the past, scrofula, or tuberculosis of the cervical lymph nodes, a common disease in children, was thought to be due to M. tuberculosis. Since 1950, many cases of scrofula due to nontuberculous mycobacteria have been reported. The disease due to the "atypical" species is now more common than that caused by M. tuberculosis (182-184).

Scrofula is seen principally in children between the ages of 18 months and 5 years. Lymph nodes near the mandible are usually affected, but infection of the parotid, inguinal, femoral, and other lymph nodes has also been reported (183). Usually the infection is unilateral and is accompanied by swelling with no associated pain. Even with scrofula, children seem to be healthy with no constitutional problems (184). The nodes may, within a short time, soften, rupture, and form a sinus with drainage. Fibrosis of the lesion may occur, followed by calcification (9, 185).

Three species of Mycobacterium are commonly involved in nontuberculous lymphadenitis; M. kansasii, M. avium complex, and M. scrofulaceum (9, 87, 184, 186). However, sporadic cases from M. szulgai and M. fortuitum-chelonei have been reported (9). Greater numbers of isolations of one species over another in certain parts of the United States have been reported. In a study conducted in Dallas, Texas, M. kansasii was found to be the dominant etiologic agent (184) and in another conducted in Cleveland, Ohio, M. scrofulaceum was the dominant agent (9). The most common species involved has been M. avium-intracellulare and the most frequent serotypes incriminated are 2, 4, 6, 8, and 9 (9, 187).

INFECTION OF SOFT TISSUE

Some 50 years ago, skin diseases associated with mycobacteria were mistakenly thought to be due to other bacteria or fungi (188, 189). They are now recognized as infections due, in large part, to MOTT bacilli. M. tuberculosis still causes some, but relatively few in comparison to MOTT bacilli. Mainly, three species, M. marinum, M. ulcerans, and M. fortuitum-M. chelonae, have been isolated from lesions of the skin and subcutaneous tissue, mostly associated with swimming pool infections (9). M. kansasii has also been shown to cause soft-tissue infection (190). M. chelonae infections have been observed in apparently healthy people as a result of DPT vaccination (191).

SYSTEMIC DISEASE

Disseminated disease caused by MOTT bacilli, mostly in immunosuppressed people, has been reported (9). In such cases, M. kansasii and M. avium-M. intracellulare-M. scrofulaceum complex and some other scotochromogens have been found to be associated with the disease (192). Systemic mycobacteriosis with hematologic abnormalities have been seen mostly in persons suffering from preexisting leukemia, leukopenia, leukocytosis, or some type of preexisting or immunodeficient disease (193-196). Disseminated infection with M. avium-M. intracellulare in homosexuals and drug users has also been documented (197). At present, there is no evidence that, as a result of MOTT bacillus infection, the immune system of the body is suppressed.

DISEASES OF BONES AND JOINTS

Infection of bones of the hand, wrist, elbow, and hip joints by various strains of mycobacteria have been reported (198). These were caused by M. kansasii and M. avium-M. intracellulare following injuries. The infections were invariably deep, and some presented carpal tunnel syndrome (199, 200).

MISCELLANEOUS

Renal disease due to M. kansasii and M. avium-M. intracellulare has been suspected but never confirmed (201-202). Infections of the meninges with M. kansasii and M. intracellulare have been confirmed by isolation of these organisms from spinal fluid (77, 203).

PATHOLOGIC MANIFESTATIONS

Detailed descriptions of the lesions in pulmonary involvement are incomplete because the available tissues were from resected lobes (9). It is thought that the gross and microscropic lesions produced in humans as a result of infection with MOTT bacilli do not differ from those caused by M. tuberculosis. In some cases the intracellular localization of Group II organisms could be very prominent (148).

Infection of the cervical lymph nodes produces characteristic granulomatous lesions. The lesions as reported are comparatively more purulent than those seen with M. tuberculosis. In other respects, the lesions in the lung and in cervical lymphadenitis, caused by both M. tuberculosis and MOTT bacilli, are identical, including eventual calcification (185).

DISSEMINATED

Generalized mycobacteriosis is rare and clinical diagnosis is almost impossible. Depending on the stage of the disease, mycobacteriosis in swine is manifested as anything from small foci in several organs to extensive nodular lesions found in the liver, spleen, lung, kidney, and lymph nodes of the cervical region or the digestive tract (14). In cases of extensive infection there may be signs indicating a chronic infectious disease, but the clinical signs are not unique. There may be a rise of body temperature, anorexia, loss of weight, dyspnea, and diarrhea. Enlargement of the lymph nodes may interfere with the functions of adjacent organs. As in cases of M. tuberculosis or M. bovis, advanced nontuberculous mycobacterial infection may cause swelling of the neck due to enlargement of lymph nodes, arthritis, mastitis, etc. (14, 44, 204).

LOCALIZED

Most of the available data on swine mycobacteriosis are derived from Federal meat inspection records. A study in 1975 found that 90 percent of suspected pathologic specimens were later confirmed by the Agency laboratories as "tuberculous lesions" (36). During this time, independent researchers reported that the principal cause of the disease in swine is the M. avium complex (table 5). The Agency record for "tuberculosis," for the years 1977-80, presented in table 9, indicates that comparatively few animals were found unfit for human consumption and were condemned. In the majority of the cases, the lesions were localized, not severe, and the carcasses were passed for cooking as required by the Federal meat inspection regulations (35).

Table 9 --Prevalence of Tuberculosis in Swine Reported by the Federal Meat Inspection Program, United States, 1977-80

Year	Total Slaughtered	Rate per Thousand			
		Suspected	Passed	Passed for Cooking	Condemned
	Number				
1977	69,945,417	7.3	6.71	0.54	0.07
1978	71,808,911	8.0	7.40	.55	.06
1979	83,323,703	7.7	7.09	.54	.06
1980	90,825,556	6.8	6.25	.51	.05

Data from Meat and Poultry Inspection, USDA (35)

PATHOLOGIC MANIFESTATIONS

The disease in swine appears to be self-limiting and is principally seen in young animals. The lesions detected at post-mortem inspection are usually limited to pharyngeal, cervical, and/or mesenteric lymph nodes. The lesions vary from pinpoint, yellowish-white, caseous foci to a diffuse enlargement of the entire node. The lesions may be observed in one node or a group of nodes, or may involve a number of lymph nodes along the digestive tract. Although there are differences in "tuberculous adenitis" of mammalian and avian origin, gross differentiation is usually difficult. With an infection of avian origin, the lymph nodes may be enlarged and firm with no discrete purulent foci. There may be one or more caseous areas with indistinct borders. Calcification is rarely observed. The lesions may have diffuse fibrosis and practically no encapsulation. At times, large areas of caseation involving an entire lymph node are seen (14, 204).

ETIOLOGY

Bacteriological studies of lesions in the United States and elsewhere indicate that most cases in swine, labeled as tuberculosis, were primarily due to various serotypes of the M. avium complex (48, 126, 127, 132, 135, 136, 141). Other studies found lesions mainly in the mesenteric, pharyngeal, and cervical nodes (116, 135, 204-210). The causative organisms generally were isolated from lymph node lesions. However, this group of organisms has also been isolated from the lymph nodes of animals that were negative to skin tests, presented no lesions in any tissue, and had no signs of illness (7).

The involvement of different serotypes of the MAIS complex in swine mycobacteriosis from various parts of the world has been discussed in chapter III.

CHAPTER V

PATHOGENICITY OF MYCOBACTERIA OTHER THAN TUBERCLE (MOTT) BACILLI

Distinction between "potential pathogens" and common saprophytes is not difficult, but not all the first group is associated with the disease nor are the latter always "saprophytes," as some are occasionally associated with disease. Most known pathogenic MOTT bacilli are probably opportunistic and only under special circumstances become pathogenic (211-214).

VIRULENCE

Certain species of these mycobacteria occasionally have been shown to produce disease in humans, other animals, or both (66, 164, 205, 215). Like all other mycobacteria, including M. tuberculosis, some species of MOTT bacilli do not always produce disease in humans or in animals. Comparatively, the "atypical" mycobacteria are less virulent than M. tuberculosis and M. bovis, but at times, have been shown to cause chronic or, seldom, even life-threatening disease in humans or animals (13, 39-41, 66, 77, 136). MOTT bacilli do not produce exotoxins or endotoxins. Their pathogenicity cannot be explained based on any single structure, antigenicity, or mechanism of action (19).

VIRULENCE OF ISOLATES FROM HUMANS

Since the discovery of pigmented acid-fast bacilli in clinical specimens in the 1950's, attempts have been made by several workers to determine the pathogenicity of these isolates. The published results have not been entirely consistent even though the majority of workers noted fluctuations in strain pathogenicity for different laboratory animals (216).

As early as 1935, photochromogenic clinical isolates from humans we : tested for pathogenicity in guinea pigs, rabbits, and chickens. Even with large doses of these organisms the reactions in animals were not uniform (145). In 1938, another isolate injected intraperitoneally produced no lesions in chickens, scattered gross lesions in the viscera of rabbits, and caused death in guinea pigs. The same results were noted with M. tuberculosis and M. bovis (217). In another study a number of photochromogenic isolates failed to produce infection in the guinea pig, although some of these isolates were found to cause lesions in the viscera of rabbits (218).

In monkeys photochromogenic and nonchromogenic clinical isolates, injected in massive doses, produced hypersensitivity but not illness (219). Studies have shown that some doses of M. scrofulaceum can produce disease in rabbits but not in mice or guinea pigs (220). Certain photochromogens, following intravenous inoculation, have shown greater predilection for kidneys than for lungs (221). In mice, "atypical" isolates produced lesions primarily in the lung and liver (216).

Pathogenicity for mammals and birds has been found to vary widely with the M. avium complex organisms. In one study, all 10 isolates examined were reported to be lethal for fowl, but only six of these were also lethal for rabbits. Another seven isolates did not produce significant lesions in fowl (222). Based on the progressive nature of lesions, the virulence of various

isolates for mice was suggested in the following manner: avian > human avian > Battey type > Group III from soil (223).

These and other reports indicate that the pathogenicity of "atypical" strains of mycobacteria is not always the same for different laboratory animals. Apart from some species differences, loss of virulence in certain strains may result from repeated subculturing in artificial medium (216).

VIRULENCE OF ISOLATES FROM ANIMALS

Variability in the pathogenicity of the M. avium complex for mammals and birds has been reported. M. avium isolates from swine were found to be highly pathogenic for chickens and rabbits but not for guinea pigs (9, 224). Strains from diseased birds, usually serotypes 1 or 2, are pathogenic for rabbits and chickens. Pathogenicity has been used as a characteristic for identifying serotypes 1 and 2, which are usually encountered in diseases of certain avians and mammals (9).

Forty of forty-three from swine proved to be fatal for chickens (224-225). The study showed that a 1 mg cell-suspension injected intravenously produced fulminating infection, killing birds within 3-4 weeks, whereas a 0.1 mg dose caused death in 6-10 weeks. Macroscopic and microscopic lesions were typical of avian tuberculosis and acid-fast organisms were recovered from the lesions. In guinea pigs, these same isolates produced localized abscesses at the site of inoculation.

Another study revealed that 64 isolates from swine (resembling M. avium) had low or no pathogenicity for fowl. It was concluded that the pathogenicity of nonchromogenic mycobacteria does not depend on their origin, but rather on their relationship to M. avium as determined by biochemical characteristics (226). Results of another study showed that M. intracellulare isolated from swine was able to produce lesions in fowl and rabbits when injected intramuscularly with a dose of 0.1 mg of cell suspension. Isolates identified as M. avium produced tuberculosis in fowl at a low dose of 0.01 mg of cell suspension inoculated intravenously (114). A majority of isolates from swine, resembling M. avium, were unable to produce lesions when injected intravenously into other pigs. All muscle samples from these injected swine were found to be free of organisms (227). In another study, 20 isolates from swine, not identified serologically, produced lesions in the livers and the spleens of chickens (52). In Sweden, five M. avium isolates from swine showed definite pathogenicity for hens, guinea pigs, rabbits, and mice and were classified under serotype 2 (228). M. intracellulare serotype 8 isolated from swine and inoculated into the mouth submucosa of swine, with a dose of 0.1 mg cell suspension, produced macroscopic tuberculoid lesions in the cervical lymph nodes of the animals in 2 weeks. With a dose of 0.01 mg, lesions were detected a month later (126). Generally a higher virulence has been observed with M. avium than with M. intracellulare, independent of natural or artificial infection (43).

INTERRELATIONSHIP OF PATHOGENICITY AND SEROTYPES

A relationship between pathogenicity and the serotypes of MAIS complex organisms has been reported (71, 229). The pathogenicity for laboratory animals, of various serotypes in the MAIS complex, is summarized in table 10.

Table 10 -- MAIS Complex Serotypes and Their Pathogenicity for Various Laboratory Animals and Man

Serotypes	Identity	Virulence for Mice	Pathogenicity for*				
			Gp	Ch	Rb	Pg	Mn
1,2,3	M. avium	Fully	-	+	+	+	**
6	M. avium (intracellulare)	Fully	-	+	+	+	**
4,5,7,9,11	M. avium "	Variable	-	+	+	+	-
8	M. avium "	Variable	-	-	-	+	**
12-23	M. avium "	Usually Not	-	-	-	-	-
41,42,43	M. scrofulaceum	Unknown	-	-	+	-	**

* Gp = Guinea pig
Ch = Chicken
Rb = Rabbit
Pg = Pig
Mn = Man

\+ = Pathogenic
\- = Nonpathogenic
** = Occasionally Pathogenic

Available sources indicate that serotypes 1, 2, and 3 are classical M. avium and usually are pathogenic for birds. The pathogenicity for guinea pigs of serotypes 4 through 23, termed as M. intracellulare is dose dependent. M. scrofulaceum, serotypes 41, 42, and 43, are reported to be nonpathogenic for mice and guinea pigs, but lethal for rabbits (72, 220, 223). In one study, 24 of 32 M. intracellulare strains isolated from human patients did not produce lesions in chickens (229). Five isolates from humans, although classified as M. avium serotypes 1 and 2, were not pathogenic for chickens, whereas serotype 10, although usually not pathogenic for chickens, was found to be pathogenic (229). In most instances, serotypes 1 and 2 isolated from birds were found to be pathogenic at least for birds, but not for all laboratory animals (73).

The serotype most commonly recovered from man and animals is M. avium complex serotype 8. Serotype 8 isolated from humans has been found to be less pathogenic for chickens than serotype 2 (72).

It appears that some serotypes of the MAIS complex are usually not pathogenic for guinea pigs, rabbits, and chickens. Some have been found to produce disease in one kind of laboratory animal, but were unable to produce lesions in a different laboratory animal. It is possible that certain predisposing factors are necessary for the organisms to cause an infection in a host. Attempts to produce disease in swine with the isolates from swine or from

their surroundings produced mixed results (43, 114, 227, 228). The pathogenicity for guinea pigs, rabbits, chickens, etc., of all other serotypes in this complex has not been studied. Some human isolates of the M. avium complex have been reported pathogenic in guinea pigs, rabbits, chickens, or other laboratory animals. Divergent findings involving M. avium-like mycobacteria may be due to injudicious selection of mycobacterial colonies (230).

CHAPTER VI

DISTRIBUTION OF MYCOBACTERIA OTHER THAN TUBERCLE (MOTT) BACILLI

Since a relationship between the " atypical" mycobacterial isolates and lesions was first postulated (145), mycobacterioses in both humans and animals have been reported (chapters III and IV). As these mycobacteria were isolated from the environment, human and animal infection from environmental sources has been suspected.

Reports of isolation of these organisms from the environment are extensive, and these have been found in virtually every reasonably hospitable environment.

WATER

There have been several reports of the isolation of MAIS complex organisms from various bodies of water. Isolations have been made from moorland water (231), swimming pools (232), lakes and reservoirs (96), accumulated rain water (233), tap water, ponds, streams, aquariums (96), well water, swamp water and an animal watering hole (234,235), and salt water (96, 236-238). One study (239) reported isolating MAIS complex organisms from 33 percent of water samples collected from various aquatic environments in the Southeastern United States. By contrast, 20 percent of the water collected in the Northeastern United States yielded MAIS complex organisms. The study also reported frequent recovery of MAIS organisms from water samples with salinities from 0.1 to 1.9 percent (239).

SOIL

A survey of various soil samples demonstrated the presence of mycobacteria in 86.1 percent of arable soils, 70.3 percent of meadow soils, and 37.5 percent of forest soils (238).

It is now thought that mycobacteria are part of the normal flora of the soil, and that their prevalence varies with the biological activity of soil (132, 240). Many serotypes of M. avium complex have been isolated from soil (241, 242). Others also have isolated "Battey-avian" like strains from soil (240). In a majority of the cases, strains pathogenic to chickens, some belonging to the MAIS complex, have been isolated from soil inhabited by mammals or birds whereas nonpathogenic strains predominate in other soils (114, 134, 241).

HOUSE DUST

Isolations of MAIS complex organisms have been made from house dust by various workers (80, 243, 244). Some investigators believe that house dust harbors the organisms and can be a potential source of human infection (80, 243). In another study, workers could not isolate any strain of the MAIS complex from 192 house dust samples (245).

WOOD SHAVINGS

Organisms belonging to the MAIS complex, isolated from swine lesions in outbreaks, were also isolated from fresh wood shavings used as animal bedding

(246, 247). M. avium organisms found in this material were suspected as the source of infection in swine (53, 61, 248), but the source of these organisms in the wood shavings could not be determined. In only one study was it determined that the wood shavings were indeed the source of organisms (247). However, the wood from which the shavings were derived was found to be sterile. From these results, it was suggested that the wood shavings may have been contaminated by dust, soil, equipment, or from the animal itself (247).

FECES

In one study, "atypical" mycobacteria were isolated from 70.5 percent of fecal samples of grazing cattle and 10.9 percent of fecal samples collected from intensively reared sows or chickens. The results also disclosed that mycobacteria are more common on plant stalks near the ground than higher up (238). It was postulated that these organisms were picked up by grazing cattle and the organisms colonized the gut of the animals. Animals such as swine or chickens that are fed prepared rations have less chance of being exposed to these organisms through feed (238).

FOOD

Isolation of mycobacteria from various human foods of animal or plant origin have been reported.

Milk: Several workers reported the presence in milk of Group III nonchromogenic mycobacteria which may have been M. avium (91, 92, 249-251). One researcher reported isolating M. avium serotypes 9, 13, and 19 from milk (93). The occasional occurrence of M. avium in milk was thought to be through contamination from the environment. It was concluded that milk is not a significant source of infection (249).

Fruits, Vegetables, and Animal Feed: Mycobacteria have been isolated from fruits and vegetables, particularly from the edible part in contact with soil. Isolates did not include any known human or animal pathogens (252). Another study showed that lettuce watered with a suspension of M. avium retained the organism even after repeated washings (253). M. avium has been isolated from animal feed stored in barns (254-255).

Oysters: Fifteen strains of mycobacteria were isolated from oysters. Only two of the strains belonged to the MAIS complex group (95).

ANIMAL AND BIRD SOURCES

In 1942, a study in Denmark showed that the avian tuberculosis infection rate was highest in chickens and tame pigeons, moderate in sparrows, gulls, pheasants and hares, and very significant in wild birds and rats (256). Avian tuberculosis in wood pigeons has been reported, but the causative organism(s) were not isolated (257). The disease has also been reported in starlings (257-258), pigeons (259), turtle doves (260), and exotic birds (261). Both M. avium and other "atypical" mycobacteria have been isolated from chicken eggs (262), pigs, cattle and hens (139), and from the environment of domestic animals (227).

MISCELLANEOUS SOURCES

M. avium serotypes 2 and 8 and the double type 3/9 were isolated from pig compost. The same serotypes were isolated from tuberculous lymph nodes of pigs. Experimental disease in pigs was also caused by feeding identical pig compost (135).

Mycobacteria belonging to Runyon Groups II and III were also isolated from 835 insect samples. M. avium (no serotype given) was most common in insects found around sawmills (263).

Mycobacteria have also been isolated from sphagnum moss throughout Europe (264, 265). Most of the isolates did not belong to the MAIS complex group. But M. avium has been shown to survive in the "gray layer" of sphagnum moss (266).

M. avium serotypes 1, 2, 7, 8, 10, 16 and 17, as well as a number of isolates referred to simply as Group III mycobacteria, have been isolated from soil, feed, bedding, and vegetation in and around farms (255).

CHAPTER VII

DISEASE CAUSED BY, AND TRANSMISSION OF, MYCOBACTERIA OTHER THAN TUBERCLE (MOTT) BACILLI

As MOTT bacilli are widely distributed in nature, a single isolation of organisms of this kind from a clinical specimen such as sputum or gastric secretion or from lesions does not necessarily incriminate the organisms as the agent of disease. It is only when typical clinical signs are observed, along with repeated isolation of mycobacteria, that a relationship between the organism and the disease is considered. Isolation of the same organism from resected surgical specimens or autopsy samples presents additional evidence for diagnostic confirmation. The criteria for concluding that infection by "atypical" mycobacteria has caused disease are: (a) clinical evidence together with isolation of the organisms; (b) repeated presence of large numbers of mycobacteria in the clinical specimen; and (c) no isolation of M. tuberculosis or any other pathogen at the time (212).

Lesions in swine are generally detected at the time of slaughter. On the basis of these lesions in cervical and/or mesenteric lymph nodes, most cases of "tuberculosis" in swine are reported (29).

DISEASE IN MAN

The portal of entry of these organisms in man is not well understood. As they have been found in milk, tap water, ocean water, dairy products, and oysters (chapter VI), they are carried into the gut with the ingested food. Depending on the condition of the host, the organisms then may or may not cause infection in the human. Presence of MOTT bacilli in the gastric washings of healthy employees in tuberculosis hospitals suggests transient colonization, perhaps by oral ingestion, of these organisms (267).

The higher incidence in humans of pulmonary infections, as opposed to infections of other tissues or glands, with M. avium complex, has been suggested to be a result of the higher rate of airborne infection (150). Another hypothesis has been suggested that the mycobacteria are taken into the oral cavity and in some instances adhere to the oral epithelium and replicate. After establishing themselves in the oral pharynx, there may be an occult episode of micro-aspiration into the lungs and, in a few susceptible hosts, infection and disease may result (268).

The primary infection may occur from aerosolized MOTT bacilli from the gut or from saliva via singing, talking, or coughing, followed by inhalation into the lung and subsequent localization and proliferation of organisms in a specific area of a damaged lung. Probably for this reason, primary lung infections are observed in adults with preexisting destructive lung disease (9). In some cases, reactivation of dormant bacilli, acquired earlier, has also been suspected. Scrofula infection of cervical nodes through the tonsils, adenoids or gingiva has been suggested. Airborne infection in these cases has been ruled out on the basis of lack of lesions in the lungs (269).

In humans, MOTT bacilli infection resulting in osteomyelitis indicates a blood-borne infection. This type of infection is rare and usually seen when the organism enters the body throgh a puncture wound. The pulmonary lesions

in adults may have a hematogenous dissemination similar to that of M. tuberculosis (148).

The process of MOTT bacilli infection in man differs slightly from that of typical human tuberculosis infection. Infection with MOTT bacilli by direct exposure is perceived only in persons who are exposed to the source of infection. Therefore, agricultural workers such as farmers, poultry breeders, farm workers, and their families are greatly exposed to the infection. As soil and water have been shown to be reservoirs for these organisms, persons who are exposed to these elements stand a higher chance of contracting infection (270). Therefore, it is postulated that most human infections with M. avium serotypes arise from the environment (270). However, this postulate is not supported in Australia (271). Another study conducted in Germany reported that birds, swine, and cattle may also be infected with these organisms from the environment. These animals, themselves, then become the primary source of infection for man (138).

Studies in the past on various sources of MAIS complex organisms have not incriminated any vertebrate reservoir (2). Instead, one study found sawdust, insects, and soil, and another found "pig compost," to be reservoirs for these organisms and the most common source of infection for humans and particularly for other animals. Both studies support inhalation and ingestion as the route of infection (137, 270).

It has been noted that human infection with MOTT bacilli is not always apparent and may not present clinical symptoms. Skin tests have shown a high frequency of reactions among healthy people in an area where the actual disease rate is low. Such an observation indicates either a high exposure rate in humans with organisms of low pathogenicity for man or a long incubation period of perhaps decades before the manifestation of the disease, just as it may occur in tuberculosis (77).

DISEASE IN SWINE

Research indicates that: (a) lesions in swine are generally local, involving the digestive tract lymph nodes, especially the cervical and mesenteric nodes; (b) swine may become infected if reared where infected chickens have been kept; (c) swine can become infected from grain contaminated with feces of tuberculous chickens or by eating infected chickens; and (d) infection can be transmitted from swine to swine by direct contact (272).

Migrant wild birds were found as reservoirs for "atypical" mycobacteria, and were thought to be responsible, through their droppings, for outbreaks and spread of diseases in both poultry and swine (258).

The frequent finding of mycobacterial lesions in the cervical and mesenteric lymph nodes in pigs suggests infection by ingestion. One survey showed that 97.3 percent of the lesions were observed in mesenteric lymph nodes compared to only 2.7 percent in the bronchial lymph nodes. The higher incidence of infection in the mesenteric lymph nodes is probably due to ingestion resulting from "rooting" type feeding habits of swine (14).

EXPERIMENTAL INFECTIONS IN SWINE

There are several reports of swine infections produced artificially with organisms administered orally with aerosol sprays, and also by keeping healthy swine in close contact with other infected swine (209, 228, 255).

By feeding poultry livers and spleens infected with M. avium to swine, development of well-marked lesions in the mesenteric lymph nodes of swine and the isolation of acid-fast organisms from these lesions were reported (273). Infection of lymph nodes of pigs by feeding or injecting M. avium complex into the lymph nodes was also reported. Intradermal injection in swine with isolates labeled as Group III mycobacteria resulted in a local response with swelling and ulceration. Acid-fast organisms were recovered from the ulcers but not from digestive tract lymph nodes (274).

In a study, it was noted that the infection rate in swine did not increase significantly by feeding grains contaminated with the feces of tuberculin positive swine (274). It was concluded that feces do not play an important role in the spread of infection. Presumably, tuberculin positive swine, from which the feces were collected, had restricted infection with no prominent lesions, and hence did not shed many organisms in the feces.

Infection in swine was produced by the oral inoculation of M. avium serotype 8. Lesions in the cervical or mesenteric lymph nodes and presence of mycobacteria in the tissue were seen (275). Infection in swine was also produced by intravenous inoculation of M. avium serotype 2 (276). With a dose of 3.7×10^7 organisms inoculated orally, no clinical signs were observed in most cases, and lesions, if at all present, were confined to the mesenteric lymph nodes. A higher dose (6.6×10^9) of serotype 2, administered orally, produced no clinical illness. But histopathologically, inoculated pigs showed activation of lymphoid tissue in the tonsils, Peyer's patches, and mesenteric lymph nodes. Also, there was evidence of spread of infection, most often in the liver, less frequently in the spleen and lungs (277).

Experimental infections in swine with MAIS complex organisms indicate that most natural infections occur through the oral route, and the intradermal introduction of MAIS organisms produces a local reaction. Experimental pulmonary infection with these organisms has never been reported.

Studies in Denmark (72, 139) indicate that natural elements in the environment, and not infected poultry, are probably the major source of infection in swine. Natural susceptibility and their "rooting" habit was suggested as contributing to a high rate of M. avium complex infection in swine. Other studies in the United States and Denmark offer support that soil and, to some extent, infected poultry are probably the main sources of infection in swine (32, 72). Evidence from human clinical cases suggests that M. avium complex infection in humans is by inhalation, whereas the evidence in swine suggests infection by ingestion.

TRANSMISSION

The mode of transmission of MOTT bacilli in man is unknown. Available information indicates that these organisms survive and multiply in the environment of man. Isolation of MOTT bacilli from animals and bird droppings led many to

suspect that animals and birds were reservoirs for these organisms and a source of infection for man and swine. Some food items such as milk, oysters, vegetables, and meat have also been proven to harbor them (252).

Person to Person: Unlike tubercle bacilli, there is limited evidence that MOTT bacilli infection in man is transmitted from person to person (9, 66, 77, 147). Although patients harboring the mycobacteria are thought to be noncontagious, there are a few incidents where suspected infections were transmitted between immediate family members, much as TB (221, 278, 279). In these cases, it was thought that patients may have spread the bacteria in their immediate environment in large numbers and the recipient host was constantly exposed to the massive doses of organisms (245).

Transmission of M. intracellulare among close family members was suggested when identical organisms were isolated from the diseased lung of an elderly man at autopsy and from resected lung tissue of his son several years later (9).

Contrary to these reports, a recent study conducted in a nursing home among high-risk groups showed a lack of evidence of person-to-person transmission (280). Resistance of these organsims to common antibiotics, enabling them to survive, has been hypothesized as possibly facilitating the spread of these organisms from patients to healthy people (281). Occurrence of atypical mycobacteria in close family members does not necessarily mean transmission from man to man. In can also suggest a common source in the environment (282).

Birds to Man: The earliest reported case of human pulmonary tuberculosis due to avian tubercle bacilli was reported in a subject who bred budgerigers 12 years prior to the onset of his disease. Another case was reported in a person who had worked for 5 months in a poultry plant eviscerating chickens (283). Another report of human infection was recorded as being the result of association with diseased birds (32). Of the three human cases reported in Australia, two were caused by M. avium type 1, and the third by serotype Davis (presently serotype 8). Only in one was exposure to chickens noted (284). An epidemiological survey by skin tests performed in Russia on 1,282 poultry workers, 120 local residents, and a group of students living in a different area indicated a high percentage of reactors among the workers and the residents but none in the student group. Although no clinical cases were reported in reactor groups, it was implied that contact with infected chickens increases the risk of contracting avian mycobacteriosis (285). A study of 65 cases in Czechoslovakia, conducted during 1965-1970, implied transmission of infection from infected chickens to man and recommended speedy eradication of tuberculosis in poultry in order to eliminate the source of infection to humans (286).

A recent report from Australia postulated that the source of M. avium, cause of a chronic pulmonary infection in a patient, was poultry, as the strain was not found free-living and had pathogenicity for chickens (287). Based on the similarity between the serotypes of human and poultry isolates, hens and free-living birds were again thought to be important sources of infection of M. avium serotypes 1, 2, and 3 (273). Infection from poultry was again suggested based on the association between man and birds in Maryland and isolation of M. avium complex organisms from 540 subjects. The intensity of

the broiler industry in the vicinity of human reactors was cited. The organisms were also detected in the broiler farm litter, soils upon which broiler litter was spread as fertilizer, broiler house water, various pine trees, soybean and chickweed, oysters, crabs, yellow perch and the waters of the Chesapeake Bay. Furthermore, identical organisms were isolated from the sputum of a retired broiler grower with symptoms of disease and also from a healthy broiler grower (288).

A study of skin sensitivity to tuberculin PPD and sensitin, and analogous preparations from M. avium, revealed a relationship between tuberculosis epizootics in poultry and the frequency of the positive reaction among the poultry plant personnel. Length of service in workers and the decreasing rate of infection in poultry had no impact on the skin sensitivity of plant personnel (289).

Swine to Man: Although, at one time, M. bovis infection in swine was thought to be high, more recent evidence indicates that almost 97 percent of the swine tuberculosis cases known today are due to the organisms belonging to the M. avium complex (37-43). Swine are, therefore, suspected by some to be a reservoir and source of M. avium complex infection for humans. Thus, natural transmission of these organisms, if at all possible from swine to humans, could be due to: (a) direct contact, i.e., handling of diseased swine by veterinarians and carcasses by butchers; (b) swine contaminating the soil with pathogens in their feces, with man inhaling the aerosolized ortanisms from the feces; and (c) as a result of swine meat consumption. There are no reports that support any of the above hypotheses on the transmission of M. avium complex from swine to man (13, 55, 255, 256).

The occurrence of MAIS complex organisms in both humans and animals does not prove transmission from animal to human or vice versa. In a study conducted in Australia, M. intracellulare was found in the sputum and in the gastric washings of deep-litter piggery workers. The same organisms previously were found to have caused mycobacterial lymphadenitis in swine. No clinical cases in humans were recorded, and M. intracellulare isolated from personnel were suggested to be a result of occupational exposure (290). The hypothesis that pork is a significant cause of human mycobacteriosis was also tested in a 1979 study. The results indicated that human infection with MAIS complex organisms did not originate from pork consumption (291).

Swine to Swine: Prevalence rates of swine mycobacteriosis have been found to be higher in some States than others. Based on the USDA Meat and Poultry Inspection retention records of swine carcasses, some of the occurrences have been marked as epizootics. In some instances, it was thought that the transmission of infection took place from animal to animal (14, 38, 204). Experimental transmission of infection from swine to swine has been documented (273, 292). In another study, swine inoculated orally with M. avium serotype 2, were found to shed the organism in their feces in 2 weeks. A group of healthy pigs, allowed to come in contact with the infected pigs, exhibited positive skin reactions, excreted M. avium serotype 2 in the feces, and later were shown to have lesions (293). In another study, pigs infected orally with M. avium had lesions in mesenteric lymph nodes and sometimes in submaxillary, bronchial, or mammary lymph nodes. Later, healthy pigs that were allowed to come in contact with the infected animals showed evidence of infection (294).

CHAPTER VIII

OCCURRENCE OF MYCOBACTERIOSES IN HUMANS AND SWINE

Since the 1950's nontuberculous mycobacteria have been suggested as a possible cause of human disease. Because of limited knowledge of the role of these mycobacteria in human infections, many of these cases were not properly diagnosed. Since then, various studies have reported human and swine infections caused by MOTT bacilli (294-301).

IN HUMANS

In the United States it is mandatory for clinicians, hospitals, and sanatoriums to report cases of tuberculosis. They are not required to distinguish between the cases by their etiology. Based on the reports from different states, the Centers for Disease Control (CDC) in Atlanta, Georgia, prepares an annual report on the incidence of tuberculosis in the United States. The data include the cases caused by MOTT bacilli.

Discrepancies in the data of these diseases may result from incomplete reporting procedures, lack of correlation between laboratory isolation procedures, or nonidentification of mycobacterial strains. Over the years, interest has increased in nontuberculous human infections, especially those caused by the MAIS complex. To determine the estimated frequency of such infections in the United States and and in other countries, surveys of cases were done by various researchers. The results are presented in table 11.

The ratio of nontuberculous cases of MAIS complex etiology expressed as a proportion of the total mycobacterial diseases varies from less than 1 percent to 30 percent (9). These estimates are based on a study of 100 cases of "atypical" lung infections in the United States where 27 percent of the cases were due to M. avium M. intracellulare (326). A study in Japan indicated that the MAIS complex was responsible for 90.3 percent of the cases (323) whereas in western Australia it was responsible for only 10 percent of the cases (324). This group of organisms was found to be responsible for 50 percent of the cases in British Columbia, Canada, and 67.5 percent in the city of Toronto, Canada (327). The prevalence rate in Toronto was five times higher than that of British Columbia (328, 329). No common factor could be identified as contributing to the higher incidence of MAIS complex infections in Rochester, New York, St. Louis, Missouri, Japan, and India (table 11).

Between 1976 and 1978, 1,839 isolates of MOTT bacilli from human infections were studied by the National Jewish Hospital and Research Center in Denver, Colorado. Almost 650 isolates belonged to the MAIS complex, and 74 percent were of serotypes 1, 2, 4, 8, 9, 12, 14, 16, and 19 (330).

In 1969, the geographic distribution of nontuberculous mycobacterial infection in the United States was estimated from skin sensitivity tests performed on Navy recruits. A high positive rate was found in the South Atlantic region. The study did not include clinical symptoms associated with any subject or isolation reports of the organisms from subjects (88).

In 1980, M. avium-M. intracellulare complex organisms were isolated from 540 residents of the eastern shore on the Delmarva Peninsula. A relationship

Table 11 -- Estimated Incidence of Mycobacterial Disease in Humans in the United States and Other Countries

Country	Region	Locality	Year	Total Mycobact. Cases	Percent Non-TB Cases	Percent MAIS Complex	References
United States	NC	Chicago	1958-61	---	3	0	(151)
		Chicago	1965	---	7	0	(149)
		Omaha	1963	167	4	0	(302)
		Cleveland	1963-76	1643	3	1.5	(303)
	NE	Rochester	1969-72	206	30	36	(167)
	SE	Lexington	1962-63	179	3	0.6	(304)
		Connecticut	1968	1610	1	0.5	(305)
		Boston	1973	---	0.5	0.4	(306)
	SW	Dallas	1960-67	---	14	0	(152)
		Dallas	1962-67	1000	11	1.9	(307)
		New Orleans I	1963-70	328	16	3	(308)
		New Orleans II	1965-70	1256	14	1	(308)
		Louisiana	1966-69	197	9	7.7	(308)
		Houston	1967	412	8	3	(309)
		Florida	1969	---	3	3	(310)
		Oklahoma	1966-68	---	--	26*	(311)
		Kansas City	1962-72	---	7	0	(154)
		St. Louis	1978	125	--	11	(312)
		Mt. Vernon	1976	---	--	20*	(313)
United Kingdom		Natl. Survey	1959	1081	0.5	0	(314)
		Hospital I	1957-66	---	1.3	0	(315)
		Hospital II	1970	75	10	1	(316)
		Sheffield	1964-73	702	5	0.3	(317)
		Wales	1971	---	7	0	(318)
U.K. and Wales		Survey	1975	---	--	9*	(319)
Germany			1971	---	--	75*	(320)
Norway			1961-65	6800	--	2	(321)
Israel			1966	60	--	60**	(322)
Japan		Natl. Survey	1979	247	--	90.3	(323)
West Australia and Queensland			1962-73	---	15	148*	(324)
India			1965-70	---	0.85	13	(325)

* Not percent (total not available)
** Photochromogens (M. kansasii) included

between the geographic distribution of these isolates and the high percentage of positive skin test in humans to PPD-B was again suggested (288).

To ascertain the distribution and the frequency of potentially pathogenic mycobacteria, CDC in 1979 initiated a survey with various States. Twenty-four of the fifty-four laboratories contacted supplied data on the isolation of all mycobacteria from diagnosed cases (331). The total number of M. tuberculosis and MAIS complex isolates from these laboratories for 1979 is presented in table 12. The most frequently encountered isolate was M. tuberculosis (68.1 percent), followed by M. avium complex (18.4 percent), and M. scrofulaceum (2.9 percent). The total frequency of the MAIS complex was 21 percent, roughly one-third of the number of M. tuberculosis isolates.

Table 12 -- Isolation Rates for M. tuberculosis and MAIS Complex Organisms from Humans Reported by Some State Laboratories in the United States, 1979*

Species	No. of Isolates	Isolation Rate**
M. tuberculosis	16,582	9.32
M. scrofulaceum	728	0.41
M. avium Complex	4,484	2.52

* Reference 331
** Per 100,000 population of reporting States.

The study also grouped these isolates by geographic area in order to show the prevalence of a particular type in a region. The data compiled from the survey indicate that the maximum number of MAIS complex ioslations was reported from the South Atlantic region (table 13). The isolates in this region were 2.3 and 2.7 times higher than the next reporting regions of Mid-Atlantic and eastern North-Central respectively. The higher incidence of MAIS isolations in the South Atlantic region corresponds with the higher rate of positive reactors in Navy recruits in the 1969 study (88). Excluding the State of Hawaii (14.97), the rate of isolation for M. avium complex per 100,000 population was also highest in the South Atlantic region, with the higher rates found in Georgia (9.07), Florida (5.77), and Maryland (5.06).

In a followup study in 1980, it was again found that M. tuberculosis accounted for 65 percent of the pathogenic isolates followed by M. avium (21%), M. fortuitum complex (6 percent), M. kansasii (3 percent), and M. scrofulaceum (2 percent). The overall isolation rate for M. avium complex for the United States was 3.2 per 100,000 population.

The rates were higher in the States bordering the Atlantic Ocean and Gulf of Mexico in the southwest and several States bordering Canada. Again the rate was highest in Hawaii (10.9), followed by Connecticut (8.9) and Florida (8.4). The study found differences in the geographic distribution of various mycobacterium species and infections they cause in the United States (332).

Table 13 -- Isolation of M. tuberculosis and MAIS Complex Organisms in Humans in Different Regions of the United States

Region	Total Isolates	M. tuberculosis	MAIS Complex		
			M. avium Complex	M. scrofulaceum	Total
			Number		
New England	837	518	237	12	249
Middle Atlantic	4,796	3,692	773	140	913
Eastern North-Central	3,669	2,437	671	88	759
Western North-Central	788	403	234	20	254
South Atlantic	8,403	5,319	1,757	349	2,106
Eastern South-Central	1,347	1,184	109	6	115
Western South-Central	2,755	2,094	240	44	284
Mountain	923	598	229	24	253
Pacific	792	337	234	45	279
Total	24,310	16,582	4,484	728	5,212

Source: Reference 331.

Increases in the frequency of diseases caused by M. avium complex have been reported from hospitals in British Columbia (327) and Illinois (333). But reports from other hospitals in northern Illinois and Ohio (9) and Brisbane, Australia (334), indicate that the frequency over time has remained fairly constant.

Based on the earlier observation that the range of cases caused by mycobacteria other than tuberculosis varies from 1 percent-30 percent of the total number of tuberculosis cases, estimates for the total number of mycobacteriosis cases for the years 1970-80 were made (table 14). The data indicate a rise in the total number and rate in 1975, but both leveled off during the next 2 years. This may be due to more precise identification of the mycobacterial species during the years 1975-77. In 1980, 27,749 tuberculosis cases were reported, an increase of 80 cases from 1979.

Estimates of mycobacteriosis cases rose from 4,140 in 1979 to 4,162 in 1980, a total increase of 12. Unlike the decreasing trend of mycobacteriosis cases in the past, this was the second time an increase was seen since 1953. The increase in the total number of tuberculosis cases seen in 1975 was the result of a change in counting criteria. The total tuberculosis case rate, per 100,00 population, decreased from 12.6 in 1979 to 12.3 in 1980. Therefore, estimates of mycobacteriosis cases for that period also decreased from 1.9 to 1.8.

Table 14 - Estimated Cases and Case Rates for Tuberculosis and Mycobacterioses in Humans in the United States, 1970-80

	Number of Cases			Rate/100,000		
Year	Total	Tuber-culosis	Mycobac-teriosis	Total	Tuber-culosis	Mycobac-terioses
1970	37,137	31,566	5,570	18.3	15.5	2.8
1971	35,217	29,934	5,282	17.1	14.5	2.5
1972	32,882	27,949	4,933	15.8	13.4	2.3
1973	30,998	26,384	4,649	14.8	12.5	2.2
1974	30,122	25,603	4,518	14.2	12.0	2.1
1975	33,989	28,890	5,098	15.9	13.5	2.3
1976	32,105	27,289	4,815	15.0	12.7	2.2
1977	30,145	25,623	4,521	13.9	11.8	2.1
1978	28,521	24,242	4,278	13.1	11.1	2.0
1979	27,669	23,518	4,150	12.6	10.7	1.9
1980	27,749	23,536	4,162	12.3	10.5	1.8

Sources: Centers for Disease Control, Tuberculosis in the United States, 1979.
Centers for Disease Control, Morbidity and Mortality Weekly Report, 1980, 29:305.

IN SWINE

Unlike human cases, no data are available on the prevalence of mycobacteriosis and tuberculosis in swine. In 1922, the USDA reported tuberculous lesions in 16.35 percent of swine slaughtered, and condemned 0.2 percent of the carcasses. The rate decreased to 1.2 percent in 1970, with a condemnation rate of 0.006 percent. The rate further decreased to 0.681 percent in 1980. Of 90,037,586 swine slaughtered that year, only 4,782 (0.005 percent) animals were unfit for human consumption and were condemned (table 2). The prevalence of the disease in the United States has been noted to vary by geographic region (table 3). For the years 1977-80, the highest prevalence was in the Southeastern and Northeastern regions. However, the condemnation rate, which depends on the progression of lesions, did not vary significantly between

regions. The States with the highest prevalence rates included Alabama, Florida, Mississippi, Delaware, and Maryland (29, 30).

In the 1930's the high prevalence in cattle of tuberculosis caused by M. bovis was thought to be responsible for the high prevalence of tuberculosis in swine (31, 46). However, reports in recent years indicate that the disease in swine is largely caused by MAIS complex organisms (chapter IV, tables 5 and 15).

Table 15 -- Etiology of Some Reported Swine Tuberculosis Cases in the United States and Other Countries

Year	Country	Attack Rate	Lesion 1/	Detected at:	Etiology	References
		Percent				
1965	Sweden	0.09	MS	Slaughter	M. avium	(228)
1966	Sweden	.84	MS	Slaughter	M. avium	(41)
1967	Sweden	.11	MS	Slaughter	M. avium	(276)
1968	Sweden	3.2 - 80.4	Lung	Slaughter	M. avium	(277)
1973	Brazil	3.1	CS	Slaughter	MAIS	(336)
1974	Poland	30.0	CS,MS	Slaughter	Atypical	(337)
1976	France	3.2	CS,MS	Slaughter	M. avium	(133)
1976	Canada	40.0 - 50.0	SB,MS	Slaughter	M. intracellulare	(128)
1976	Belgium	NA	Intestine MS	Post-mortem	M. avium	(48)
1977	Czechoslovakia	88.0	MS	Slaughter	MAIS	(43)
1977	Sweden	39.0	CS,MS	Slaughter	M. intracellulare	(42)
1978	Norway	33.0	SB,MS	Slaughter	MAIS	(338)
1978	Brazil	14.8	CS,MS	Slaughter	MAIS	(127)
1978	Austria	100.0	NA	Slaughter	M. avium	(339)
1979	Japan	NA	MS	Slaughter	MAIS	(60)
1979	Germany	41.7	SB,MS	Slaughter	MAIS	(340)
1980	Brazil	4.4	NA	Slaughter	MAIS	(210)
1973	U.S. (Iowa)	2.8	CS,MS	Slaughter	NA	(341)
1975	U.S. (S. Dakota)	NA	CS,MS	Slaughter	M. avium	(37)
1976	U.S. (Iowa)	91.0	CS,MS	Slaughter	M. avium	(40)
1976	U.S. (Georgia)	88.0	CS,MS	Slaughter	M. avium	(38)
1978	U.S. (Georgia)	84.0	CS,MS	Slaughter	MAIS	(134)
1979	U.S. (Arizona)	97.0	CS,MS	Slaughter	M. avium	(61)

1/ Lesions:
MS = Mesenteric lymph node
CS = Cervical lymph node
SB = Submaxillary lymph node
NA = Information not available

In some instances, an attack rate of 97 percent was observed based on the lesions in lymph nodes and was reported as an epidemic (61). In only a few instances was disseminated disease reported and the animal carcasses declared unsafe for human consumption (335). Generally, the lesions are confined to the cervical or mesenteric lymph nodes. Otherwise, the animal presents no signs of illness and the majority of the carcasses examined are declared safe for human consumption (29, 35, 36).

MAIS-infected swine look healthy on ante-mortem examination, but at post-mortem examination may have lesions in the lymph nodes of the cervical or mesenteric regions. Symptomatic mycobacteriosis is seldom seen in swine. Reported cases, therefore, are not based on clinical signs, but on the lesions observed at their post-mortem examination (table 15).

In 1962, when tuberculosis caused by M. bovis was prevalent in cattle in Germany (FRG), only 14 percent of the infections in swine were due to M. avium. By 1979, the rate had increased to 93 percent (340). However, the M. avium infection rate of 90 percent in swine in South Africa for this period remained fairly constant (193, 311). In an outbreak of M. avium serotype 6 in swine in Toowoomba, Australia, in 1967, lesions were observed in 67 percent of a total of 1,768 animals slaughtered. About 13 percent of the infected carcasses and an additional 13 percent of the heads were condemned. None of the swine had clinical signs of illness (342). Followup studies showed the presence of MAIS organisms in water troughs and deep litter, which were thought to be sources of infection (80). In comparison, the rate in the United States has remained fairly constant (table 15).

The available evidence indicates that the prevalence of MAIS complex infection in swine, over the years, has remained fairly constant. In contrast, as opposed to the belief of the 1950's that the "tuberculosis" lesions in swine were due to M. bovis, the present evidence indicates that the majority of such lesions are caused by MAIS complex organisms.

CHAPTER IX

EPIDEMIOLOGY OF MYCOBACTERIOSES IN HUMANS AND SWINE

Recent studies on skin sensitivity in humans indicate that infections with MOTT bacilli are common in many areas in the tropics and are quite frequent in the temperate zones. Clinical reports of such infections indicate that the frequency of these infections in humans has increased (chapter IV). Concurrently, the occurrence of M. tuberculosis and M. bovis infection has decreased (chapter VIII). The available data indicate that the prevalence of M. tuberculosis, M. bovis, and MAIS complex infection in swine has decreased (chapters IV and VIII).

Limited data on the diseases caused by MAIS complex organisms do not definitely prove man-to-man transmission. Artificially induced disease in swine has been shown to be transmitted by contact from one animal to another by contact. However, there is no evidence that the disease is transmitted naturally from swine to swine or between swine and humans. The pathogenicity of MAIS complex organisms varies for individuals, particularly for those with decreased immune response (343). In a controlled study, a subject with M. intracellulare disease did not transmit the disease to other members in a nursing home for the elderly in spite of continued close contact between them (280). Although studies have shown that many foods such as milk, cheese, oysters, and vegetables carry MOTT bacilli (chapter VI), none of the foods has ever been incriminated as a source of infection (chapter VII). It appears, therefore, that humans and other animals acquire infection from environmental sources other than food, animals, or other infected persons (chapter VI).

IN HUMANS

The two species of mycobacteria other than M. tuberculosis most frequently demonstrated to be agents of human disease are M. kansasii and M. avium complex.

Sex: The disease may occur in persons of either sex. A Georgia study indicates that M. avium and M. kansasii most often attack older males from a rural environment (157). However, the disease has been recorded in infants and females (279). The incidence rate was reported to be 4.9 for white males compared to 2.9 for white females per 100 person-years. In Blacks, a 0.1 percent higher rate was seen in females than males (344). In an analysis of 166 infected patients in East Germany, 95 percent of the patients were males. A majority of the male patients had occupational exposure to dusts of various kinds and to chemical irritants (320).

Race: Negroes appear to have more resistance to nontuberculous infection than do Caucasians. An analysis of the data on "atypical" infections in various ethnic groups indicates that of the total patient population, only 5 percent to 24 percent of the infections occurred in Negroes (66). In a study based on 100 person-years, a significantly higher rate of 4.9 was observed in Caucasians as compared to 2.9 for Negroes (68, 344).

Age: Usually, nontuberculous mycobacteriosis is seen in persons over 40 years of age and, frequently, in those over 50 (9, 320, 344). One study found 57

years to be the median age among the patients (280). However, the disease has been reported in persons less than 40 and in infants (279).

Occupation and Other Diseases: Several researchers tried to relate the significance of occupation, susceptibility to infection, chance of exposure, and other diseases resulting from one's occupation. A study revealed that 36 percent of the patients with "atypical" infection had a history of working in the lumber industry, a source of sawdust, which is reported to support the survival of pathogenic mycobacteria (340). Exposure to fibrogenic (quartz) or nonfibrogenic (ash, lignite, cornmeal, flour) dust, chemicals (formaldehyde, chlorine), and regular contact with animals have also been reported as predisposing occupational factors that favor infection. In a majority of the cases there had been a long-term exposure (20-year average) to these injurious elements or animals. In some patients no relationship between occupation and infection could be established (320).

Controversy exists regarding the impact of a person's occupation on the chance of becoming infected. Direct infection arising from occupation has been strongly argued (43, 45). The greater possibility of infection in agricultural workers and their families, or in persons working on poultry farms (chapter X), has also been considered (345, 346). Other persons, such as rubber workers, coal miners, and those engaged in dusty trades or welding, have been shown to be more susceptible to infections of the MAIS complex organisms (280, 347).

Concurrent systemic or pulmonary diseases such as silicosis (348-350), pneumonia, and tuberculosis (66) were frequently recorded in some patients with MAIS complex infections. Other diseases commonly associated with this infection are chronic bronchitis, emphysema (166), or any condition which damages the lung (149, 303, 351) or that has lowered the immune response of the body, such as in acquired immune deficiency disease (AIDS) (343).

Geography: There have been repeated reports of MAIS complex infections from the Southeastern United States (239, 267, 352), western Australia (80, 241, 244), and Japan (125, 126, 245, 323). One study demonstrated a higher rate of skin sensitivity to PPD-B along the coastline of the Eastern United States, with the prevalence decreasing with the distance inland. The study also indicated that organisms are spread by the wind and the wave action of the sea, both of which are dependent on weather conditions (352).

Individual Variations: As in tuberculosis, in most infections caused by MOTT bacilli, the local immune response curtails the multiplication of bacilli and limits their location to small foci. Such sites may remain dormant without any further spread. Except for these lesions, most exposed individuals present positive skin test results with no clinical or pathological consequences. Some individuals are less able to control the foci of infection and the organisms multiply in the host, with subsequent clinical disease. Many attempts have been made to identify and characterize the basic immunologic and pathologic factors that account for such differences in individual resistance to mycobacterial infections (25). It is not well understood how the immunologic responses of one normal human differ from those of another, in accounting for the differences in susceptibility to, and the clinical consequences of, mycobacterial infection. Disseminated infections have been thought to

result from an immunologic imbalance in the host (77). Such infection was observed in a case of fatal, disseminated disease in a child following BCG vaccination (353).

Malignancies: The association of tuberculosis with malignancies has long been recognized. An analysis of recorded cases points to a definite relationship between cancer and M. kansasii infection. A review of the literature indicates that the risk factor associated with malignancies for both tuberculous and nontuberculous infection is approximately the same (9, 312).

Immunosuppressive Agents: Cytotoxic drugs may profoundly depress the cellular immune system and allow invasion by various infectious agents, including mycobacteria. The effect of immunosuppressive drugs and chances of infection in heart transplant cases are thought to be quite significant. It has been noted that patients undergoing cytotoxic therapy for malignant disorders develop mycobacterial infections more often than those who have not been treated with cytotoxic drugs (354).

Other Risk Factors: Various other factors have been suggested that may influence a host's susceptibility to mycobacterial infection. Nutrition (355), poor hygienic standards and mode of living (279), intravenous drug use and homosexuality (197), eating habits, such as eating raw eggs, thumb sucking, and close contact with poultry and pet birds (345) have all been suggested as contributing to infection.

IN SWINE

Contact: Direct contact between swine and chickens has been suggested as a possible cause of M. avium infection in swine (14). Likewise, M. bovis infections in swine were attributed to direct contact with infected cattle (46).

M. tuberculosis infection of swine in the U.S. and abroad was suggested to be a result of direct or indirect association with human patients (31, 47, 117, 118, 123, 126). There are no records that MAIS complex infection in humans resulted from direct contact with swine.

Age: Except for breeding stock, pigs are usually slaughtered at 5 to 7 months of age. There is no evidence to indicate a relationship between the presence of single or multiple lesions and the age of an animal.

Geography: During the 1940's the highest number of cases was recorded in the North-Central States of the United States (32, 356). It was thought that the higher incidence in swine in these areas was related to the higher rate of disease in poultry (14). However, in recent years the rate of avian tuberculosis in all regions, including the North-Central States, has decreased. Comparatively, the rate in swine in the North-Central States has declined but remained somewhat higher than in other regions (29).

Miscellaneous Factors: M. avium infection in swine has been related to rearing pigs where infected birds were reared (272, 356) and also to feeding inedible (for humans) portions of tuberculous chickens (64). M. bovis infection in swine has been attributed to feeding cattle offal and unpasteurized

milk (46, 50). Tuberculosis has been observed in swine when they are allowed to consume feces, unpasteurized milk, and uncooked garbage from hotels and, particularly, from hospitals (13, 14).

As suspected in the case of human infections, imbalanced nutrition in swine may make them more susceptible to infection. The environment, such as closed piggeries with sawdust used as bedding, may also contribute to swine infection (227). A higher prevalence of the disease in certain breeds has been considered but not conclusively proven (14).

CHAPTER X

PREVENTION OF MAIS COMPLEX INFECTION IN SWINE

In recent years it has become evident that M. bovis and M. tuberculosis infections in swine have decreased or nearly disappeared (chapter II). Most swine infections labeled "tuberculosis" today are due to the MAIS complex organisms (chapters III, IV, and VIII) that are frequently encountered in the environment (chapter VI). These are considered to be the source of much of the mycobacterial infection in swine (71, 72, 80, 95, 96, 357).

DETECTION

MAIS complex infections in swine generally do not produce remarkable clinical signs from which a diagnosis can be made. Only if the infection progresses over a long period of time may the animals show signs of disease. Most swine that exhibit lymph node lesions detectable during meat inspection do not present any clinical symptoms, and appear healthy during antemortem examination (36).

Since 1906, several studies designed to evaluate the use of the tuberculin test in diagnosing swine "tuberculosis" have yielded variable results (14). According to some investigators, tuberculin skin tests using avian and mammalian tuberculins provide information useful in herd diagnosis of tuberculosis in swine (50). The procedure requires an intradermal injection of 0.1 ml of mammalian tuberculin (USDA-OT) in one ear base, and 0.1 ml of avian tuberculin (Avian-OT) in the opposite ear base (PPD tuberculins of corresponding biologic activity can also be used). A similar test is made on the vulva of sows. The reaction (induration) at the injection site usually reaches maximum intensity after 48 hours. The swelling of the site is then measured. In swine infected with MAIS complex organisms the swelling observed to avian tuberculin usually reaches twice the size of the swelling due to mammalian tuberculin. Repeated skin tests may be necessary to identify those animals which have a new infection. Sometimes positive reactions have been encountered where calcified lesions are present (50, 58).

VACCINATION

The control of swine tuberculosis with BCG vaccination was advocated long ago, especially against M. bovis infection. Although protection has been reported by some investigators (62, 358), BCG vaccination failed to protect animals against disease in well-controlled studies (359, 360). It is not known whether such vaccination has any protective capacity against MAIS infection in swine. However, some scientists are of the opinion that antibodies developed in swine due to natural MAIS infection provide some protection against mammalian tuberculosis (14, 50, 145).

PREVENTION

To control the spread of MAIS complex organisms from a source and to reduce the chances of swine being exposed to these organisms, the following procedures or practices have been recommended by various investigators (14, 46, 47, 64, 204, 256, 257, 260, 261, 285, 361):

1. Swine should not be allowed in contact with diseased humans.

2. Efforts to eliminate tuberculosis in cattle and poultry should continue.

3. Swine production operations should not be started in an area where avian tuberculosis has been observed nor in close proximity to an area where tuberculosis occurs in cattle or poultry.

4. Unpasteurized milk and dairy byproducts should not be fed to pigs.

5. Swine should not be fed raw offal from abattoirs, or uncooked garbage, especially from hospitals.

6. Wild birds which may act as carriers of mycobacteria must be controlled.

7. Swine should not be fed grains that may have been contaminated with feces of tuberculous chickens.

8. Tuberculin-positive animals should be eliminated to control the transmission of disease from animal to animal.

9. Sawdust bedding for deep-litter piggeries should be avoided.

10. Strict sanitary practices should be followed in swine production operations.

11. If large numbers of pigs on a farm or in an area are affected, look for a source and eliminate it.

Depending on the circumstances, any one or more of the above measures will be more suitable in preventing the disease on a farm (283).

ERADICATION

At present, there is no national program in the United States for the control of swine mycobacteriosis as there is for the control of bovine tuberculosis. Efforts have been made previously by the Animal and Plant Health Inspection Service (APHIS), U.S. Department of Agriculture, to involve States in a joint program to control tuberculosis in swine (361).

Present evidence (chapter VIII) indicates that tuberculosis caused by M. tuberculosis and M. bovis in swine is no longer a problem. Although MAIS complex infections are seen in swine, the etiologic agent for such infections is almost impossible to eradicate. The main source of infection with MAIS complex organisms is the environment (362).

CHAPTER XI

ANALYSIS OF THE SWINE TUBERCULOSIS PROBLEM

Since Mycobacterium tuberculosis was first found to be responsible for tuberculosis in humans, the generic name "Mycobacterium" has generated fear among people. Fear of the organisms is not always unfounded. One organism in this genus, Mycobacterium leprae, causes leprosy, a dreaded disease of humans. This organism, however, is not known to produce infection in any animal except the armadillo under natural and experimental conditions. M. lepraemurium, another species of lepromatous mycobacteria, only causes disease in the field rat.

TUBERCULOSIS AND MYCOBACTERIOSIS

Technically, the term "mycobacteriosis," in both man and swine, can be applied to all infections caused by all species of mycobacteria. Sometimes, mycobacterial infections in both man and swine are referred to as tuberculous infections; e.g., an infection caused by M. tuberculosis. Some people are of the opinion that, as a result of infection with M. tuberculosis and M. bovis a tubercle is seen as the manifestation of the disease. Because of this pathological implication the disease is called tuberculosis, and the organisms are called tubercle, or typical, mycobacteria (chapter II). Some think that it is more the transmissible clinical disease which is connected with the term "tuberculosis" than the pathological or histopathological reaction in the form of a tubercle (362). With other mycobacterial diseases (chapters III and IV), especially the infections by MAIS complex organisms, no primary tubercle is found. Thus, these organisms are referred to as nontuberculous mycobacteria, or mycobacteria other than tubercle (MOTT) bacilli, and the infection as "mycobacteriosis" (chapters III and IV).

According to one researcher, the difference between tuberculosis and mycobacteriosis is not the existence or nonexistence of a "primary tubercle," but rather the onset of pathogenesis by the respective mycobacteria (362). In any case, it is evident that the manifestations of the diseases, tuberculosis and mycobacteriosis, caused by the two groups of mycobacteria, in humans and in swine, respectively, are different (chapters II and IV).

TUBERCLE MYCOBACTERIA

M. tuberculosis, principally a cause of lung disease in humans, is transmitted to swine primarily by the alimentary route. Swine are usually infected by this organism as a result of ingesting uncooked garbage contaminated with sputum from tuberculosis patients, especially if such garbage comes from hospitals or sanitariums (chapter IX). Because of improvements in swine husbandry practices in recent years, M. tuberculosis infections in swine are rare (chapters III and IV).

Since 1889, tuberculosis due to M. bovis has been observed in cattle, domestic animals, and wild animals (31-33, 46-52, 363). M. bovis infections in swine result from feeding unpasteurized milk from infected cows (363). In the 1930's it was suggested that most tuberculous lesions in swine were due to M. bovis and originated from diseased cattle, and that the occurrence of the disease (lesions) in swine would decrease if the infections in cattle were

properly controlled by the national tuberculosis eradication program. Since the program started, the "tuberculosis" rate in both cattle and swine decreased over the years, but the decline in swine, as compared to cattle, was less (chapter II).

The presumption that M. bovis caused swine tuberculosis in the past was based, not on the isolation of the causative organism, but on the gross lesions. As discussed earlier (chapters III and IV), the lesions of M. tuberculosis, M. bovis, and MAIS complex organisms are grossly indistinguishable. In recent years, most disease in swine, confirmed by culture isolation, was shown to be caused by MAIS complex organisms (chapter VIII). Therefore, it is likely that a majority of the tuberculosis lesions in swine which were previously thought to be due to M. bovis were probably due to MAIS complex organisms.

MYCOBACTERIA OTHER THAN TUBERCLE (MOTT) BACILLI/MAIS COMPLEX ORGANISMS

Since Koch's discovery of the tubercle bacillus in 1882 as the etiologic agent for human tuberculosis, other mycobacteria have been reported to cause diseases of birds and animals. Additionally, isolation of several nonpathogenic mycobacteria has been reported from birds and animals and the environment (chapters III and VI).

At one time the prevalence of classical tuberculosis in humans and animals was so overwhelming that the possible involvement of other mycobacteria, aside from the known few, was completely overlooked. However, investigations over the past three decades have identified other mycobacteria as causative agents of disease in both humans and animals. Thus, the present concern is not confined to M. tuberculosis or M. bovis and their involvement in lung and extrapulmonary diseases, but includes other mycobacteria that can cause pathologic processes in a number of different organ systems in humans and animals (chapter III). These organisms isolated from clinical specimens from humans and animals and from environmental sources, are generally referred to as mycobacteria other than tubercle (MOTT) bacilli. Consequently, diseases associated with this group of bacteria have been referred to as nontuberculosis, mycobacteriosis, mycobacterial infection, atypical mycobacteriosis, etc.

A group of MOTT bacilli, M. avium complex (M. avium-M. intracellulare) and M. scrofulaceum, together known as the MAIS complex organisms and different from M. bovis and M. tuberculosis, have been known to cause disease primarily in birds and, occasionally, in humans, swine, and cattle (chapters III, IV and VII). In the 1940's it was suggested that most tuberculosis lesions in swine were the result of M. bovis, and some were due to M. tuberculosis infections. As discussed earlier, such opinions, which were based on the gross lesions, apparently were not sound. Even today, the total number of cases reported as swine "tuberculosis" by USDA, MPI, are not differentiated as to their etiologic agent (table 2). Recent evidence indicates that in the majority of cases in swine, MAIS complex organisms can be accurately and specifically isolated from the lesions (39, 48, 81, 134, and tables 5 and 15).

Like M. tuberculosis and M. bovis, these organisms are slightly curved or straight rods or coccobacilli, have high lipid content, and stain acid-fast by Ziehl-Neelsen or fluorochrome procedures. In the 1950's, microbiologists attempted to classify the different species of mycobacteria, including

M. tuberculosis and M. bovis, by their growth rate and need for special growth conditions. Additionally, some of the species were further identified by their capacity to produce pigment when exposed to light. Those which produced yellow colonies only in the presence of light were grouped as photochromogens or yellow bacillus. Those which produced yellow-orange colonies both in light and in the dark were called scotochromogens. The others which did not produce any pigment at all were labeled as nonphotochromogens (83, 149, 164). Some of these latter strains have been referred to as Battey bacilli, because many of the organisms from this group that resemble M. avium were first isolated from human patients in Battey Hospital in Rome, Georgia (280).

Serological techniques have been used to differentiate the species of M. tuberculosis, M. bovis, and M. avium. Strains of M. avium were further divided into three groups by agglutination and complement fixation tests (364). Later, other researchers utilized serologic techniques to investigate M. avium-like organisms (365-367). The presently recognized serotypes of MAIS complex organisms, by agglutination test, are shown in table 6 (98, 367, 368). Serotyping is one of the accepted methods for the final identification and differentiation of MAIS complex organisms. MAIS complex antigens have been recognized by immunodiffusion and immunoelectrophoresis (369).

MYCOBACTERIA, THEIR HOSTS AND SITES OF INFECTION

There are many species in the genus Mycobacterium that have heterologous hosts. M. leprae is an exception. It infects humans but not any other animals except the armadillo under natural conditions. Both M. tuberculosis and M. bovis can infect humans and other animals, including swine, but neither of these species has been shown to cause natural infection in chickens. M. avium, which causes tuberculosis in chickens, can also infect humans and swine.

Classical tuberculosis in humans due to M. tuberculosis is primarily a disease of lungs with specific pathologic manifestations. However, the infection in swine, either by M. tuberculosis or M. bovis, is manifested in the gastrointestinal tract and in the related glands and organs (chapter II). The lesions in swine due to MAIS complex are usually confined to the mesenteric lymph nodes (chapter IV). The MAIS complex infection in adult humans has been observed in various tissues such as lungs, bones, and soft tissue. In children, it has been shown to cause lymphadenitis or "scrofula," an infection of the maxillary lymph nodes (chapter IV). Therefore, the site of infection in humans and swine, caused by this group of organisms, is different.

MYCOBACTERIOSES IN HUMANS

In the 1900's, the incidence of typical tuberculosis caused by M. tuberculosis in man was so prevalent that the presence of MOTT bacilli in clinical specimens and their role in the disease were given little consideration. Before 1960, these organisms were seldom identified and incriminated for the diseases of various tissues and organs in humans (chapter III). Since then, these organisms have been found to occasionally be responsible for human mycobacterioses in the United States and various other countries of the world (chapters III and VIII). Out of the total infections by MOTT, the percentage of infections caused by MAIS complex organisms ranges from 2 percent to 20 percent (chapter VIII).

The majority of the disease caused by MAIS complex organisms in humans is respiratory and the lesions seen are in the lung (chapter IV).

At present it is not mandatory for clinicians, hospitals, and sanitariums to distinguish cases of human mycobacteriosis from those caused by M. tuberculosis or M. bovis. A 1982 survey of isolates from State health departments in the United States indicated that 21,286 tuberculosis cases were caused by M. tuberculosis. Of the total, it was estimated that only 2,000 cases were due to MAIS complex organisms (332).

MYCOBACTERIOSES IN SWINE

In the 1950's, as a result of poor husbandry practices, occasional infections by human and bovine tubercle bacilli were reported in swine (31, 47). Presumably, M. tuberculosis infection of swine resulted from feeding uncooked garbage, whereas M. bovis infection resulted from feeding unpasteurized cow's milk, and also from allowing swine to come in contact with diseased cattle (46, 370). With improvements in swine husbandry practices and effective measures to control bovine tuberculosis, M. tuberculosis and M. bovis infections in swine are rare (tables 5, 7 and 15).

In the 1930's M. avium infections in swine were reported to be due to exposure of swine to infected birds, feeding infected birds to swine, and housing swine on M. avium infected soil (272). In the 1940's the higher rate of M. avium infection in swine in the U.S. Corn Belt was thought to be directly related to the higher rate of tuberculosis in poultry (14). However, MAIS complex infections in swine also occurred in places where the prevalence of M. avium infection in poultry was low (13).

M. bovis infection in swine, though currently rare, has been observed in the past to be serious, rapidly progressive, and fatal. M. tuberculosis infection, also seldom seen in swine, is less severe and less rapidly progressive. In contrast, clinical symptoms are rarely seen in swine with MAIS complex infection. The indications of infection noted at the time of slaughter are lesions occurring mostly in the cervical and the mesenteric lymph nodes. Some researchers feel that if the severity of the infection is an indication of the etiology, then swine that are noted to have lesions of this nature at slaughter do not have M. tuberculosis or M. bovis infection (371).

In 1980, some 90 million swine were slaughtered in the United States, with no evidence of mycobacterial infection during the ante-mortem inspection. During post-mortem examination, only 0.005 percent of the swine carcasses were condemned as a result of mycobacterial lesions. Absence of clinical signs, less severe lesions seen during post-mortem examination, and past etiologic reports (chapters II and IX) suggest that nearly all cases in swine reported in the past by the Meat and Poultry Inspection Program, USDA, as "tuberculosis" cases were, in fact, due to MAIS complex organisms. In a majority of the cases, confinement of the lesions to the lymph nodes of the gastrointestinal tract further indicates that such infections in swine are by MAIS complex organisms (371). Actual data on the prevalence of mycobacteriosis in swine confirms that a majority of cases, as high as 97.5 percent reported as TB cases, could be identified as caused by MAIS complex organisms (Chapter VII).

MEAT INSPECTION REGULATIONS FOR MYCOBACTERIAL LESIONS IN SWINE

Current disposition criteria for tuberculosis in swine are based upon the recommendations set forth in a report to the USDA by a special committee of the Department of Health, Education and Welfare (HEW) in 1972 (372) that was reaffirmed in 1976 (373).

A synopsis of the regulations is:

(1) Carcasses with lesions in only one system (the cervical or the mesenteric lymph nodes) are passed for human consumption after removal of the affected part (head or gastrointestinal tract).

(2) Carcasses with lesions in two organ systems (usually cervical and mesenteric lymph nodes) are passed for cooking (PFC). The carcasses must be cooked to 170°F for 30 minutes before they enter the food chain.

(3) Carcasses with lesions that involve organs like the liver are considered to have a generalized infection and are condemned.

The regulations allow PFC carcasses to be used in meat food products after the carcasses are heat treated, or the product may be heat treated after the PFC addition. Since PFC carcasses have limited use, small operators who do not have the facilities to cook such carcasses discard them (36).

Since cooking at 170°F for 30 minutes greatly limits the market for PFC carcasses, studies have been conducted to find an effective method to kill the mycobacteria present in these carcasses with less stringent heat processing. These studies showed that a combination of time/temperature treatment procedures other than the prescribed 170°F for 30 minutes could make PFC carcasses safe for human consumption (374-376).

ROLE OF SWINE IN HUMAN MYCOBACTERIOSES

THE MAIS complex organisms consist of 32 serotypes, all of which have been isolated both from sick and healthy humans or swine. Because some serotypes of the MAIS complex, particularly serotypes 1, 2, 4, and 8, have been associated with disease of both humans and swine (chapters IV and VII), swine have been suspected of being a source of human infections. However, since 1960, the incidence in humans of disease by MAIS complex organisms has not changed significantly (chapters IV and VIII), even though during this period the per capita U.S. consumption of pork fluctuated (29).

Two theories have been advanced to explain the epidemiolgical basis of the MAIS complex infections in man and swine. First, some persons have speculated that swine are the reservoir of this group of mycobacteria and that these can be transferred to humans either by direct contact or through the ingestion of pork muscle (7, 8, 139, 377-379). However, there is no recorded evidence that man has ever contracted MAIS complex infection from swine through the handling or ingestion of pork, or from contact with swine. Similarly, there is no record that man has ever contracted M. tuberculosis or M. bovis infection from swine contact or ingestion of pork. Of further significance to this is a recent study that failed to associate pork consumption with human sensitivity to MAIS complex antigens (291).

The second theory is that mycobacteria are picked up by the swine from the soil and that the organisms get trapped in the lymph nodes and may or may not cause a localized reaction (357). This may very well be true as many researchers have isolated MAIS complex organisms from lymph nodes of swine with and without visible lesions (31, 209, 226, 340, 357). Thus, some people are of the opinion that the environment is the reservoir of MAIS complex organisms and that both humans, affected by some predisposing factor such as a debilitating disease, and swine are somehow infected via the environment, and that swine are not the source of MAIS complex infection of humans (95, 270, 380-385).

CHAPTER XII

DISCUSSION

The general belief of most medical scientists and the swine industry is that the lesions caused by MAIS complex organisms and seen in swine during the post-mortem examination, are not a public health hazard. Based on past data and reports it is pointed out that the swine lesions are not true "tuberculosis" lesions caused by M. tuberculosis or M. bovis and that there is no evidence to indicate that human infection originates from either live animals or from handling or ingestion of pork. They also point to the fact that there is little or no evidence confirming swine mycobacteriosis as "true infections" and that the condition would probably never cause clinical symptoms even if the animals were allowed to live. They contend that these so-called lesions are merely indications of exposure to these organisms. However, some people believe that MAIS complex organisms cause disease both in humans and swine. They are also of the opinion that swine are the possible reservoir of MAIS complex organisms and the cause for the recent apparent increase in nontuberculous disease of man (7-9, 52).

ZOONOSES

Unlike brucellosis or other zoonotic diseases associated with handling of infected meat, there is no proof that human mycobacterioses is caused by MAIS complex organisms or acquired as a result of the handling or consumption of infected pork. If these organisms were transferred from swine to humans by contact, then the rate of mycobacteriosis should be much higher among swine farmers, veterinarians, meatpackers, Federal inspectors, butchers, and cooks because these are the people who are intimately and regularly exposed to swine or pork by every possible route, including inhalation, direct contact, mucosal contamination, and accidental inoculation. Employees and inspectors in a swine slaughterhouse are subject to particularly great exposure because all the tissues that may bear lesions are palpated and sliced. It is of great significance that there is no evidence that the rate of MAIS complex infection is higher in these people.

SOURCE AND EXPOSURE

A high rate of skin reaction in humans to PPD-B in certain areas of the United States has been reported. It has been suggested that these rates are the result of exposure to MOTT bacilli, especially MAIS complex organisms, that are known to be present in soil and water (chapter IX). Repeated findings of mycobacteria in wood shavings or sawdust indicates a life support system for the organisms that is independent of animals. It is possible that certain chemicals or sugars in the sawdust support the growth of these organisms.

It is interesting to note that the MAIS complex organisms isolated from soil, water, sawdust, milk, etc., belong to many serotypes (chapter VI). In many cases some serotypes isolated from these sources have been implicated in infections of humans and swine. The serotypes isolated from different environmental sources in a country do not indicate a prevalence pattern for any particular serotype. The prevalence of different serotypes varies not only with the environmental elements, but also with the different countries.

The presence of these organisms in nature indicates that they are not fastidious in their growth requirements, and appear to survive in a changing environment by deriving nutrition from natural organic sources. Poultry, soil, water, and vegetation have also been thought to be possible sources of MAIS complex organisms for those residents of the area routinely exposed to such sources (chapter IX). Although exposure of such persons could be demonstrated by skin test reactions, it is significant that none ever presented clinical symptoms (288).

In two human cases, the same serotype of M. avium, now identified as a MAIS complex organism, was isolated from birds as well as from humans. Both humans presented clinical signs. Only in these instances has a possible association been established between these two hosts. In another instance, a known serotype in the MAIS complex was found responsible for an outbreak in a swine piggery in Australia. The same serotype was also isolated from the sputum of all the piggery workers, although none of the workers ever presented clinical signs of illness (80). In another study conducted in the United States, the same serotype was also shown to be present in healthy persons never exposed to swine (386).

These facts tend to indicate the ability of MAIS complex organisms to occur as saprophytes in humans and swine, or to act as pathogens depending on predisposing factors. Present evidence indicates that the environment is the common source for this complex group of organisms for all hosts (78, 270, 352, 385, 387, chapter IX). Like swine, man may be merely an intermediate host for these organisms. There is no proof that organisms originating from swine infect and produce disease in humans (chapter VII), even though the same serotype of organism encountered in swine has also been isolated from cases of human mycobacteriosis. Finally, Koch's postulates, the principles that would establish a relationship between this group of organisms and human disease, have never been fulfilled (343).

PREDISPOSITION AND INFECTION

There are several predisposing factors which may make certain individuals susceptible to MAIS complex infection. Infection rates have been found to vary with sex and race. In contrast to the lower prevalence of tuberculosis in Caucasians than in blacks, the highest incidence of mycobacteriosis is seen in white males over 40 years of age. In blacks, the incidence is slightly higher in females (344). In ethnic groups such as Indians or Eskimos, a higher rate of tuberculosis by M. tuberculosis has been observed (19). However, unlike tuberculosis, the rate of "atypical" tuberculosis does not vary significantly among people with different ethnic backgrounds or religious beliefs that forbid the consumption of pork (66).

A relationship between the occurrence of mycobacteriosis and the length of exposure of the host to soil (95), water (96), and other natural elements known to support the growth of mycobacteria has been suspected. A slightly higher rate of infection in agricultural workers has thus been attributed to continued exposure to soil (95, 387). Similarly, the high frequency of skin sensitivity to M. intracellulare antigens in people living on the southeastern seacoast of the United States has been attributed to the close proximity to sea water, survival of organisms in sea water, and the spread of these organisms by wind (78).

Disease caused by MAIS complex organisms has also been associated with other occupations such as mining, and with predisposing diseases such as silicosis and lung cancer. The resistance of the body is lowered under these conditions, allowing mycobacteria to colonize and possibly produce secondary infection. Use of chemotherapy in some disease conditions eliminates other pathogens in the lesion and leaves only the drug-resistant mycobacteria. In these conditions the nontuberculous mycobacteria may be mistakenly incriminated as the primary cause. In reality, many times the presence of these mycobacteria has no pathogenic consequence for the host (68, 77, 145, 147, chapter X).

Many researchers have considered nontuberculous mycobacteria, including MAIS complex organisms, as being "opportunistic," causing sporadic infections as seen with Proteus, Pseudomonas, and other organisms that rarely cause human infections even though contact with them occurs daily. Since MAIS complex organisms seldom cause infection in the host, it is perhaps justifiable to categorize these microorganisms as occasional, opportunistic pathogens (212-214). It is not known precisely why certain groups of humans are more susceptible to these infections. However, there are two theories. One theory is that certain individuals are more susceptible to the infection because of impaired immunity. This may very well be true because the rate of MAIS complex infection is higher in people on immunosuppressive drugs or affected by immunosuppressive diseases (354). The other theory is that as a result of excessive antibiotic therapy, the normal flora of the body is slowly eliminated, allowing MAIS complex organsims, which are often resistant to many antibiotics, to survive, multiply, and cause infections. However, there are no reports to support this theory.

Nutritional deficiencies and debilitating conditions due to aging have also been suggested as predisposing factors in human mycobacterioses (355). However, researchers in this area do not support any relationship between nutrition or age alone and mycobacterioses (77).

SWINE AND HUMAN INFECTION

There is no documented evidence that implicates swine as a source or carrier for the MAIS complex organisms that are responsible for mycobacterioses of humans (270). In fact, there is strong evidence that supports the opposite view that swine are not a source of MAIS complex infection in humans (291, 357, 388, 389). In addition, there is much circumstantial evidence that the environment is the reservoir and possible source for the MAIS complex infections in both humans and animals (78, 139, 239, 283, 390). These organisms can adapt to the changing conditions of an environment, can survive and multiply (239, 383, 387), remain in soil, water, and vegetation, and then can be the source of infection for both man and animals (77, 385).

Isolation of MAIS complex organisms from different environmental sources suggests that humans are exposed regularly to these organisms. It is believed that exposure to, and infection by, these organisms sensitizes people to certain mycobacterial antigens. It has been observed that sensitivity in persons living in different parts of the United States differs more with the kind of organisms to which they are exposed than to the incidence of exposure (391). Results of skin testing in Navy recruits with histoplasmin, mammalian tuberculin (PPD-S), and other antigens prepared from a "Battey"

" strain (PPD-B) illustrates the point (392). The frequency of reactions to PPD-B in the Southwestern United States ranged from 33 to 43 percent much higher than the PPD-B reaction frequency in lifetime residents of the Northeastern United States. Furthermore, cross-reaction to tuberculin is reported to be more prevalent in some areas than in other areas (88, 392). Reaction rates of 10-12 percent to PPD-B were found in the North and West, with gradually increasing frequencies towards the Southeast, where rates of 70 percent and more prevailed (391, 392). Based on several research reports it was thought that the vast majority of reactors acquired their sensitivity to PPD-B through exposure to, or infec-tion with, M. intracellulare (88, 320, 392). Variation in the rate of nontu-berculous disease of humans according to geography was noted in a recent study in the United States (331, 332). The study analyzed the data on MOTT isolates from some hospitals. There were significantly more isolates re-ported from hospitals in the South than from hospitals in the North (332).

Using skin tests or the presence of MAIS complex organisms in the sputum as acceptable methods for the determination of the rate of human disease caused by these organisms is controversial. Data on such findings with other organisms would indicate that these are not valid methods for determining disease rates attributable to these organisms. Groups of people in certain areas of the United States show skin test reaction to Histoplasma capsulatum antigen or to TB (PPD-S) without ever showing clinical symptoms of histoplasmosis or tuberculosis. Candida is found in otherwise normal females without clinical symptoms of candidiasis. Obviously, reaction to skin tests or the presence of MAIS complex organisms in a specimen does not necessarily indicate the disease, but does indicate contact with the organism (392).

Researchers reported isolating the same serotypes of MAIS complex organisms from swine and from sick and healthy humans (38, 55, 67, 133, 135, 330, 393, 394). Consequently, swine have been suspected as a possible reservoir and carrier of these organisms. However, serologic differences in these isolates present some interesting differences in the epidemiology of MAIS complex infections of man and swine. Of the 32 serotypes known in the MAIS complex group, the same serotypes have rarely been isolated from from both swine lesions and from human clinical specimens. It has been shown that the most frequently isolated serotypes in swine are not the same as those most frequently isolated from human infections.

Isolation data for the MAIS complex (table 8) indicate that serotype 2 predominates in swine from the United States, Poland, France, and Germany, whereas serotype 8 predominates in swine from Japan and Brazil. An early study on MAIS complex isolates from humans reported that serotypes 1 and 2 occurred in 10 percent of the cases in the United States and that serotype 14 was predominant. Later studies found serotype 8 as the most encountered human isolate in the United States (9,330). Such serotype differences in the isolates from humans and swine have also been reported from France (139), Sweden (132), South Africa (393), Japan (395), and Germany (396).

In contrast to the numerous isolation reports from lymph nodes, there are only a few reports of MAIS complex organisms being recovered from pork muscle (7, 377). In fact, many reports indicate the absence of MAIS complex organisms in the muscle, but indicate the presence of organisms in lymph node lesions (127,133, 142, 210). Experimentally, it has been shown that MAIS complex

organisms inoculated intravenously in large numbers did not produce infection and could not be isolated from the muscle of swine (357). The conclusion drawn from this study was that human infections with these organisms did not derive from swine (270, 388, 389, 394, 396).

Some persons believe that eating muscle from swine, with or without lesions in the lymph nodes, can cause MAIS complex infection in humans (8, 377, 378). However, a recent study showed that human skin testing reaction to antigen prepared from MAIS complex organisms did not increase as a result of pork consumption. Therefore, it was concluded that the muscle of swine carcasses, with or without mycobacterial lesions in the lymph nodes, is free of MAIS complex organisms, and that human exposure and infection is not through pork consumption (291).

Another interesting comparison can be made that has bearing on the question of whether raw or rare pork is the source of mycobacterial infection in humans. It is well known that a significant number of subclinical human trichinosis infections occur in the United States because of consumption of rare pork (397). Rare or raw pork consumption should also result in a higher incidence of human mycobacterial infection than is presently found. Consequently, there should also be no difference between skin test reactions from one region to another. However, this is not true (88).

Several studies of cervical lymph nodes of swine demonstrated that the number of apparently normal lymph nodes that contained mycobacteria was approximately equal to those with grossly visible lesions (55, 133, 142, 356, 398, 399). These carcasses, with apparently normal lymph nodes, had been passed for use as food. In spite of the fact that similar lymph nodes are being allowed regularly into the food channels, there is no evidence that pork consumption affects the incidence of human infections. Therefore, pork consumption must have no effect on the incidence of human MAIS complex infection. It would have an effect only if these organisms, under normal conditions, are capable of colonizing, and being pathogenic for, reasonably healthy humans (357, 400).

ECOLOGY OF MAIS COMPLEX

All of the available evidence indicates that the environment, rather than swine, is the reservoir and source of infection for both humans and swine. Various serotypes of MAIS complex organisms have been isolated from soil, sawdust, dust, salt and fresh water, oysters, milk, and also from bird feces in different countries (table 16). Some findings indicate that these organisms are quite adaptive to the available environment and thus may have flexible nutritional requirements (387).

Mycobacteria isolated from soil have not been conclusively proved to be the cause of human illness (95). In one study MAIS complex organisms from dust were found to have different metabolic processes than those associated with human disease. Therefore, the author concluded that human pathogens were unable to survive in dust (243). However, other researchers have reported similar biochemical reactions for the human and soil isolates (240). The marked similarity of acid-fast bacilli isolated from soil and animals has been suggested as the proof that these agents of disease in man and lower animals originate in soil (404).

Table 16 -- Source of Various Serotypes of MAIS Complex Organisms in Different Countries

Source	Serotype	Country	References
Water	1,6,7,8,14,18 19,20,23	United States, Germany, Australia,	96,231,234 401,402
Moorland Water	2,8	Germany	231,253
Salt Water		United States (East)	241
Soil	4,6,7,9,13,14 16,17,18,19	United States, Australia	133,239,241
Sawdust	3,4,6,8,10,14 16,6/8	United States, Australia, Denmark	53,80 247
Dust	6,7,8,9,12,14	Australia	244,403
Feces	3,10	Germany	238
Frog	8	United States	40
Oyster	9,16	United States	93
Milk	9,13,19	United States	93

The influence of low environmental temperature was evident when no isolation of MAIS complex organisms could be made from soil in areas from which birds migrate during the winter months. However, during the summer months these soils occasionally, and bird feces frequently, yielded this group of organisms. These observations suggest that survival of these organisms depends on the condition and the temperature of the soil and that the chances of survival are better in birds than in soil (405, 406). It was found that simple nutritional requirements of many mycobacteria could be met by bird droppings. The ultimate source of nutrition for these mycobacteria is thought, by some, to be agriculture dust or the droppings of birds which have fed on soil insects (407).

In general, survival, multiplication, and isolation of MOTT bacilli, especially MAIS complex organisms, in various natural elements suggests that the growth requirements for these microorganisms are not rigid. They appear to survive on available nutrients and can adapt to changing conditions such as fluctuations in pH, temperature, and chemical composition of natural elements (96, 232, 264, 266, 401).

Isolation of these organisms from water, especially their multiplication in water at a certain pH, suggests that some strains are more adaptive to water and have greater flexibility in surviving at variable pH (231, 253). Survival of certain strains in rain water tanks suggests strain specific multiplication and the capacity to derive simple nutrition from rotting vegetation (401). Available salt, or the plants that grow in salt water, have been found to serve as the nutritional source for these organisms (96, 401). Higher rates of isolation of MAIS complex organisms from eastern U.S. waters may have resulted from better survival of these organisms due to the chemical composition and temperature of the water and the chemistry of the nearby soil and vegetation (78, 239, 383).

CONCLUSION

Evidence indicates that two kinds of mycobacterial disease may occur in swine: tuberculosis, caused by mammalian tubercle bacilli; and mycobacterioses, caused by mycobacteria other than tubercle (MOTT) bacilli, which include *Mycobacterium avium-M. intracellulare-M. scrofulaceum* (MAIS) complex organisms. MAIS complex organisms, especially serotypes 1 and 2, have been found associated, in rare cases, with pulmonary disease of humans, resembling tuberculosis caused by mammalian tubercle bacilli, and have been isolated from swine gastrointestinal lymph nodes with or without lesions. The incidence in swine of tuberculosis by *M. tuberculosis* or *M. bovis* is so insignificantly low as to constitute no measureable health hazard.

Swine (for commercial use) are raised generally on a large scale as a unit. The animals are not allowed to come in contact with other mammals and are not fed unpasteurized milk or dairy products. The tuberculosis lesions in this type of swine are seen exclusively in the head and mesenteric lymph nodes. Under these circumstances, it is argued that involvement of tubercle bacilli is most unlikely (371). The majority of the cases in swine today, that are now reported as "tuberculosis," are caused by MAIS complex organisms and the condition should be identified as "mycobacterioses."

Transmission of MAIS complex organisms from swine to swine is rare. Transmission of these organisms from swine to humans through the handling of animals or through consumption of pork has never been documented. Therefore, it seems highly unlikely that swine are the source of MAIS complex infections in humans. Rather, there is strong evidence that both humans and swine become infected from a common source, the environment (408).

Many reports indicate that the pathogenicity of these organisms is variable and that the organisms are "opportunistic," causing infection only under special circumstances (211-214, 409). In many instances, these organisms have been isolated from healthy humans who never presented signs of illness. However, these organisms have been observed to cause illness in persons who previously had (or have) some other ailment such as silicosis or cancer, or in people who have been immunologically compromised, such as AIDS patients (408). Therefore, under normal circumstances these organisms are rarely pathogenic for man and are not health hazards to healthy humans (385).

Contrary to the hypothesis (7-9, 377, 378) that swine are the reservoir for MAIS complex serotypes 1, 2 and 3, and are responsible for the disease in humans, present evidence (285, 384, 388, 396) indicates that, other than birds and poultry, no animal is the maintenance host for these serotypes. There is no evidence that swine are a true reservoir of these organisms and swine have never been incriminated as a source of human infection.

Differences in the ratio and kinds of MAIS complex serovars involved in human and swine diseases further strengthen the contention that swine are not the source for human infections. In most countries the predominant serovars involved in swine diseases are MAIS complex organism serotypes 6 through 12, whereas serotypes 1 and 2 predominate in human infections. In the United States only 6 percent of the cases in swine were due to serotype 1, and 4 percent were due to serotype 2. In South Africa, involvement of serotypes 1, 2 and 3 were even lower than in the United States (393). Thus, the common serotypes involved in swine and human disease are not the same.

All available evidence indicates that swine are not incidental hosts, but rather occasional hosts, and that MAIS complex infection of humans does not originate from swine. In a majority of cases, the organisms responsible for the lesions in swine are serotypically different from those encountered in human disease. Apparently, both swine and humans are constantly exposed to this group of organisms, abundantly present in the environment. In some people, with certain predispositions, organisms from this source may cause infection and disease.

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